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CONTENTS

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THE QUARTERLY JOURNAL OF MEDICINE

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Ousting Superstition

Once, to cure their ailment, epileptic sufferers walked in the evening twilight to a well near Wrexham, washed there and threw fourpence in the water. Then, carrying a fowl, they passed thrice round the well and thrice round a neighbouring church, reciting paternosters. Next, entering the building, they crept beneath the altar, where they spent the night with a Bible for pillow and the bird as bed companion. At dawn they rose, left the bird in the church and made a further money offering.

This ceremonial has long passed into discard, yielding place to scientific treatment. Science, indeed, now holds unquestioned sway in therapeutics, and in all fields of medicine progress is seen to lie along the paths of disciplined research. At the Wellcome Laboratories such research is unceasing; its fruits are found in the wide range of specialities which Burroughs Wellcome & Co. supply. Many of these—such as Digoxin, 'Aerosporin', 'Histantin', 'Daraprim' and Globin Insulin—originated in the Wellcome Laboratories and are today prescribed throughout the world.

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WILLIAM OSLER

from the portrait painted in 1908 by Stephen Seymour Thomas

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Osler's account book contained the following note, dated 28 May 1915. 'Completed to-day ten years in Oxford . . . I have not done much in the profession here, but I have done 3 useful things, or better, helped to. (1) The Assoc. of Brit. Phy. (2) The Quarterly Journal of Medicine. (3) The Historical Section of the Roy. Soc. Med. . . .'

1907–1957

WITH the present number, the *Quarterly Journal of Medicine* enters on its fiftieth year of publication. An account of the early history of the *Journal* and of the Association of Physicians will be found in the Address by Sir Russell Brain printed on page 3.

It may be added that the notion of a new journal, which ultimately became the *Quarterly Journal of Medicine*, began in the last decade of the nineteenth century when A. A. Kanthack, A. E. Garrod, and W. Hale-White 'met together in order to find a means of issuing a medical Journal which would publish papers that were hardly likely to appeal to the mass of the profession, but which ought to be published as being concerned with the advancement of medical science'. The death of Kanthack in 1898 was a severe blow to this project, and it was not revived until Osler's visit to Oxford in 1904. There can be little doubt that the translation of the idea into action was mainly due to Osler. For the 12 years that he was an Editor of the *Journal* he was 'indefatigable in encouraging its growth, shaping its policies and smoothing out its difficulties'.

The business arrangements for the management of the *Journal* at the outset were typically Oslerian. W. O., accompanied by the young A. G. Gibson, dashed into the office of the Clarendon Press, and said to the then Secretary: 'We are going to have a new medical Journal, and he [pointing to Gibson] will look after it.' To Gibson he said (indicating the Secretary): 'If you want anything, ask him', and dashed out again. These informal arrangements worked with surprising smoothness, and Gibson continued in office as Secretary to the Editors for 30 years.

The following have served as Editors:

William Osler
John Rose Bradford
Archibald Edward Garrod
William Hale-White
Humphrey Davy Rolleston
Robert Hutchison
Thomas Renton Elliott
Francis Richard Fraser
Alexander George Gibson
John McNee
John Alfred Ryle
Donald Hunter
Owen Lambert Vaughan de Wesselow
Arthur William Mickle Ellis
John Crighton Bramwell
Walter Russell Brain
William Donald Wykeham Brooks

Hugh Leslie Marriott
Derrick Melville Dunlop
Robert Platt
Alexander Macdougall Cooke
Denis Hubert Brinton

The following have served as Secretary to the Editors:

Alexander George Gibson
Alexander Macdougall Cooke
Hugh Alexander Robertson

The success of a journal, and indeed its very existence, depends on the exertions of contributors, printer, and publisher, co-ordinated by the editorial board. The Editors of this *Journal* count themselves unusually fortunate in their contributors, and are deeply appreciative of the never-failing help received from both the printing and publishing sides of the Clarendon Press. It remains only to thank the subscribers and other readers of the *Journal* for their support, and to assure them that the Editors will continue their endeavours to maintain the standards and ideals of the founders of the *Journal*.

THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

Address to the Association at its 50th Annual General Meeting (1956)

By SIR RUSSELL BRAIN

This year is the 50th anniversary of the first meeting which led to the foundation of our Association, and also the 50th year of its existence. It was therefore suggested that I might open the proceedings by giving you a brief account of the Association's history.

Its origin was recorded by Herringham in the minute book immediately after the minutes of the first meeting. 'A wish had often been expressed', he wrote, 'that some magazine could be started in this country, on the lines of one or two foreign magazines, in which papers which, though scientifically important, were not suitable for the Journals, nor for the clinical or pathological societies, could be published. In May 1906 Professor Osler came to London and met at my house Garrod, Hale-White, Rose Bradford, Rolleston, and Hutchison. He agreed to help in starting such a magazine, and suggested the Clarendon Press as publishers. He also suggested the formation of a National Association of Physicians, somewhat on the lines of the Association of American Physicians, which would both be a pleasant gathering, and also should form the nucleus of a public for the magazine. The suggestion was warmly received, and it remained to see how best to carry it out. We, the above gang, first approached the Regius Professors of Medicine and the President of the Royal College of Physicians. They agreed to write to other Professors of Medicine throughout the country.'

The next step was the circulation to Professors of Medicine throughout the country of a letter signed by Allbutt, Gibson, Little, Osler, and Douglas Powell, asking them to join with the signatories in issuing a general invitation in order to start the Association. The Professors being favourable, a further letter was sent out, with 20 signatories, inviting the original members to form the Association. The invitation went in the first instance to all the acting members of the medical staffs of hospitals connected with recognized medical schools. The acceptances were so numerous that it soon became clear that the original number of 200 could not be adhered to, and in order to include all men actively engaged in research, whether attached to teaching hospitals or not, in the spring of 1907 the invitation was sent out to other physicians, some engaged in general practice and others as consultants not attached to recognized schools. Again there were many acceptances, and the original members numbered nearly 250.

The first Annual Meeting took place on Thursday and Friday in Whitsun week on May 23 and 24, 1907, at the rooms of the Royal Medical and Chirurgical Society, 20 Hanover Square, London. John Hay recalls how Osler stood on the

steps in the front of the building and greeted every member as he arrived. Sir Richard Douglas Powell, the President of the Royal College of Physicians of London, was voted into the Chair, and the first business was to pass the draft rules of the Association, of which the first was: 'The Association shall be called the Association of Physicians of Great Britain and Ireland. Its objects shall be the advancement of internal medicine, and the promotion of friendship among physicians.'

The first officers of the Association were: President, Sir Richard Douglas Powell; Treasurer, Dr. Hale-White; General Secretary, Dr. Herringham; while the Committee consisted of Allbutt, Rose Bradford, Michell Clarke, Greschfeld, Osler, Rolleston, Cowan, Fraser, Gibson, Magee Finny, Lindsay, and Little.

The first scientific meeting consisted chiefly of reports of cases, together with a clinical demonstration. Rarely can a meeting of the Association have dealt with so many original contributions destined to find a place in medical history. 'Dr. Mackenzie of Burnley related several cases, observed for a great number of years, in which the evidence of auricular systole preceding ventricular, which had been originally present, disappeared leaving ventricular systole alone apparent. The evidence of auricular systole was partly from auscultation (presystolic murmur) and partly from the existence of an auricular wave upon the venous sphygmogram. He argued that the disappearance of the auricular systole was caused by disease of the sinoauricular muscular node, which left the auriculoventricular node as the starting point of the cardiac contraction. A very lively discussion ensued.' Osler described cases of multiple hereditary telangiectases with recurring haemorrhages. Head 'demonstrated the tracks of the sensory impulses, showing how the impulses which as coming from the surface of the body were threefold (muscular, protopathic, and epicritic), were in the spinal cord recombined and formed different groups'; and Hutchison reported cases of suprarenal sarcoma in children with large metastatic tumours in the skull.

The first year's accounts showed that there had originally been 248 members, one of whom had resigned from ill health. On the credit side is an entry of '1/6, three members paid 6*d*. each too much'.

The second meeting, which was held at Edinburgh in 1908, included a discussion on chronic infective endocarditis. Horder reported that this was usually due to a streptococcus, but occasionally to influenza or staphylococcus or pneumococcus. Douglas Powell asked if the painful red spots were supposed to be embolic, and Osler replied that he believed the tender points to be due to minute capillary emboli.

Steps were taken at the first meeting of the Association to establish a journal, which was first described as the Archives of Medicine. At a meeting of the Executive Committee, to which Garrod and Hutchison were also invited, it was agreed that negotiations should be opened with the Clarendon Press for its publication, and that the Archives should be edited by a committee composed of Osler, Rose Bradford, Garrod, Hutchison, Rolleston, and Hale-White, who should be assisted by a body of 20 to 30 collaborators, whose duty should be partly to act as local centres, and partly to act as referees for papers. It is not

clear how the original title came to be altered, but there was evidently some discussion about it. By April 1908 the Executive Committee had resolved that it was desirable 'that some notification appear on the title page of the *Quarterly Journal of Medicine* showing its connection with the Association', and at the Executive Committee a month later Osler proposed that it was inadvisable to alter the title of the *Quarterly Journal of Medicine*, and this proposal was carried.

In 1911 the Executive Committee decided that to pass any resolution on the National Insurance Bill would be outside the sphere of work of the Association. Scientific business included papers by Mackenzie on nodal rhythm and auricular fibrillation, and a demonstration by Lewis of the string galvanometer for registering cardiac movement. Head and Holmes discussed lesions of the optic thalamus. The only illustration in the minute book appears in 1913. It is a photograph of two members engaged in a struggle, one wearing a top hat. It has the legend: 'The Secretary collecting subscriptions or Bart's v. Guy's—taken by John Hay.' The wrestlers are Herringham and Hale-White.

Only formal business meetings of the Association were held during the First World War. When scientific meetings were resumed in 1919 there was a noticeable change in the programme. Whereas before the war almost all the discussions had taken place on reports of individual cases, or a very small number of cases, after the war general topics greatly outnumbered case reports. In 1920 epidemic encephalitis made its appearance in the reports, and Ryle read a paper on the investigation of gastric function by means of the fractional test meal. In 1923 the use of insulin was discussed by five members representing the five insulin centres. It would be invidious to mention individual communications of more recent date, which in any case will be within the memory of many members. The history of the Association continues to record the accepted advances as well as the discarded ideas of medicine.

The Second World War presented a greater problem to the Association than did the First. Nevertheless it was possible to hold the annual meetings until 1944, when the Executive Committee decided that in view of the restrictions on travelling the whole Association should not meet. The usual annual election of new members, however, took place by postal ballot. Arthur Hurst was to have been President in 1944. The Secretary evidently took the view that the Association did meet in that year, if only in a Pickwickian sense, for the meetings continued to be numbered serially as though it had done so.

In 1951 the Association faced the problem created by the increase in the number of eligible candidates for membership, and resolved to increase the number of ordinary members from 250 to 350 and, not without regret, to require ordinary members to retire at the age of 65. This was a necessary sacrifice if the Association were to remain at a reasonable size, and only if it does not become too large can it fulfil its second object, 'the promotion of friendship among physicians'. 'The advancement of internal medicine' may look as though it no longer needed much stimulus: indeed, internal medicine now recalls a character in one of Stephen Leacock's stories, who 'galloped away in all directions'.

Let us look for a moment at the future of the Association in the light of the changes which have taken place since its foundation, especially recently. These are, in the main, three. Medicine has expanded so much that there are now in the National Health Service 2,000 consultants who practise general medicine or a medical specialty. These specialties have their own Associations, and sometimes speak a language which is unfamiliar to everyone else. Within general medicine a new generation thinks in terms of an applied science which has grown up since the older amongst us qualified. This Association surely has an important part to play in helping us to understand each other better, and in focusing common problems from different points of view. Indeed, we recognized this when we decided to give the 'symposium' a trial, but I wonder whether we ought not to give more thought to the question whether our scientific programmes are the best that we could arrange.

William Osler was our founder. We, perhaps, take the Association for granted, but it was he who overcame the medical isolation of the different parts of the British Isles, which had previously existed, and brought the physicians of Great Britain and Ireland together. And we who knew him recognize the impress of his personality still in the friendly informality which has always been so striking a feature of our meetings.

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DEFECTS OF RENAL TUBULAR FUNCTION IN THE NEPHROTIC SYNDROME[1]

Observations on a Nephrotic Child with Aminoaciduria, Glycosuria, Polyuria, Tubular Acidosis, and Potassium Depletion

By S. W. STANBURY and D. MACAULAY

(From the Departments of Medicine and Child Health, University of Manchester)

With Plate 1

It is generally considered that in the nephrotic syndrome the renal tubules retain their functional integrity even when their histological appearance is abnormal. The tubular reabsorption of such substances as sodium, chloride, and water may be nearly complete, indicating an absorptive efficiency no less than that of normal renal tubules. The commonly used tests of tubular function, such as the ability of the kidneys to produce a concentrated urine or to excrete *p*-aminohippurate, give normal results until the renal disease is far advanced (Bruck, Rapoport, and Rubin, 1954). On the other hand, an occasional nephrotic patient who appears to be otherwise typical is found to have impairment of one or more specific tubular functions. The lesion may be present when the patient is first examined, and no satisfactory explanation for its occurrence is forthcoming. Farr and MacFadyen (1940) and Glagov (1953) reported the occurrence of aminoaciduria in some patients. Blainey (1954) studied two adult nephrotic patients with gross aminoaciduria in whom the plasma levels of amino-nitrogen were normal. Although the aminoaciduria was increased by an increased intake of protein, it seemed probable that the renal tubular reabsorption of amihoacids was defective; this probability was increased by the finding of renal glycosuria in each patient. Woolf (1955) has briefly mentioned having seen aminoaciduria and glycosuria in nephrotic children. Jackson and Linder (1953) found renal glycosuria in a four-year-old child developing the nephrotic syndrome after acute nephritis but, because of the presence of extrarenal congenital defects, they considered the renal glycosuria to be congenital. The most bizarre and best documented of these complications of the nephrotic syndrome has been reported recently by Tegelaers and Tiddens (1955). They described two children with apparently typical nephrosis who were dwarfed, 'osteoporotic', and liable to attacks of tetany. Each patient had renal glycosuria, aminoaciduria, acidosis, and low plasma levels of potassium; one patient had polyuria as well as oedema. It is not yet clear whether such patients are to be regarded as belonging to some nosologically distinct disorder that might with advantage be separated from the amorphous mass of the 'nephrotic syndrome',

[1] Received February 27, 1956.

or whether the development of tubular malfunction represents a complication of nephrosis that is perhaps avoidable, remediable, or of prognostic significance. In the present communication we record our findings in a child who has been observed from the beginning of his illness. At its beginning the illness differed in no way from classical nephrosis, but the child ultimately developed a clinical condition that was identical with that described by Tegelaers and Tiddens (1955). It was possible to date fairly precisely the onset of certain specific tubular defects, and at least one potential cause for the development of tubular disorder was recognized.

Case Report

Bobby J., the third child of healthy parents, was born normally at term in March 1950 after an uneventful pregnancy. When three months old he was circumcised at the Duchess of York Hospital for Babies, and appeared then to be a normal child. Subsequent development was satisfactory until July 22, 1952, when his mother noticed that his face was puffy. On the following morning the facial swelling was worse, and he was found to have swollen legs and a distended abdomen. There was no history of respiratory infection or other disturbance before the onset of oedema. On admission to hospital the same day, he was found to be an ill child with anasarca and a tightly distended abdomen. The blood-pressure was 100/70. There was some injection of the pharynx, and the right ear-drum was pink. The urine contained a large amount of protein (3·5 gm. per 100 ml.) and a few finely granular and hyalo-cellular casts, but no appreciable number of red cells. The blood-urea was 24 mg. per 100 ml., serum-cholesterol 625 mg. per 100 ml., and serum-proteins 4·5 gm. per 100 ml. (albumin 2·2 gm., globulin 2·3 gm.). Plate 1, Fig. 4 shows the appearance of the child about a week after admission to hospital, in which time there had been no appreciable change in his condition. He was considered to be a typical case of the nephrotic syndrome, and his progress in the next year was characteristic of that disease. The biochemical changes and principal clinical events of the next two and a half years are summarized in Fig. 1.

Great difficulty was experienced in controlling the oedema, and the child remained in hospital from July 23, 1952, until August 7, 1953. Among the therapeutic procedures resorted to were repeated infusions of quadruple-strength plasma, low-salt and high-protein diet, cortisone, and cation exchange resins. The plasma infusions produced an occasional modest diuresis that was never maintained for more than a day or so. Cortisone was given in a dosage of 150 mg. daily for seven days, and then discontinued because of marked increase in the amount of oedema and general worsening of the child's condition. Resin therapy with 'katonium' was continued for the greater part of the year, with occasional interruptions because of vomiting. The daily dose varied from 15 to 45 gm., the usual dose being 30 gm. daily. Throughout the year there were repeated episodes of respiratory infection, which were treated with antibiotics. On discharge in August 1953 the boy was active and cheerful, and there was very slight oedema. The blood findings at that time were: blood-urea, 58 mg. per 100 ml.; serum-proteins, 4·9 gm. per 100 ml. (albumin 1·6 gm., globulin 3·3 gm.); serum-cholesterol, 512 mg. per 100 ml.; serum-sodium, 144 mEq. per litre; serum-potassium, 3 mEq. per litre; serum-bicarbonate, 15 mEq. per litre; serum-chloride, 104 mEq. per litre. The significance of the low bicarbonate and potassium levels was not appreciated, and no steps were taken to deal with the abnormality.

During the following six months, when he was seen as an out-patient, the child's condition remained fairly good; the oedema fluctuated, and there were further respiratory infections from time to time. On February 20, 1954, he complained of tingling pains in his hands and feet, and shortly afterwards could neither stand nor use his hands. He was admitted to hospital with typical

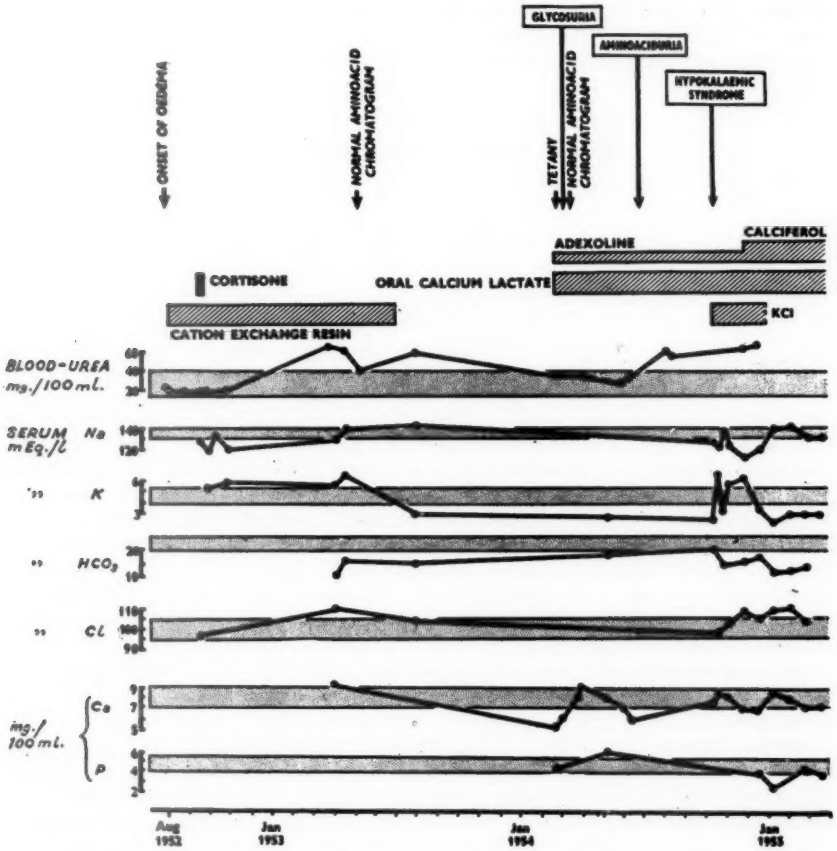

FIG. 1. The treatment, principal clinical events, and biochemical changes during the first two and a half years of the child's illness.

Details of therapy are given in the text. The stippled areas indicate the normal range of the biochemical variables charted; in the case of serum-calcium a 'normal' range appropriate to the degree of hypoproteinaemia is used.

carpopedal spasm, and the serum-calcium level was found to be 5·1 mg. per 100 ml. With a serum-protein level of 5·8 gm. per 100 ml. the calcium figure indicated a value for ionized serum-calcium of approximately 2·4 mg. per 100 ml., which is well within the range in which tetany occurs (McLean and Hastings, 1935). The Sulkowitch test gave no precipitate in the urine. The tetany responded promptly to calcium gluconate given intravenously, and the child fell asleep shortly after the injection was finished. He was subsequently

treated with calcium lactate by mouth (2·7 gm. daily) together with 'adexolin' (15 minims daily ≏ 2,000 i.u. vitamin D). The serum-calcium level rose temporarily to 9·2 mg. per 100 ml. (see Fig. 1), and there was no further tetany after the first day. On March 2, 1954 a reducing substance was detected for the first time in the urine, after the examination of many scores of specimens in the preceding 18 months. This substance was identified by chromatography as glucose, and since its first appearance it has been found in every urine specimen tested. That this was 'renal' glycosuria seems certain from the fact that during one week the fasting blood-sugar ranged from 70 to 127 mg. per 100 ml., while

TABLE I

Glucose Tolerance Tests (March, 1954)

1. *Oral glucose tolerance test:*

	Hours after 22·5 gm. glucose by mouth				
	0	*½*	*1*	*1½*	*2*
Blood-sugar (mg./100 ml.) . .	100	172	164	190	168

2. *Intravenous glucose tolerance test:*

	Minutes after 6 gm. intravenous glucose						
	0	*2*	*15*	*30*	*45*	*60*	*90*
Blood-sugar (mg./100 ml.) . .	127	360	288	220	132	114	82

Glucose was present in the urine before and after each test.

the daily output of sugar in the urine was always greater than 2 gm. An oral glucose-tolerance test revealed a high lag-curve, but an intravenous glucose-tolerance test gave a normal result (Table I). The onset of glycosuria can thus be dated exactly in this patient, and at the time there was no pathological aminoaciduria. An aminoacid chromatogram, run when the urine was examined chromatographically for sugars, showed a normal pattern, small amounts of alanine, glycine, and serine being present. An earlier aminoacid chromatogram, done in May 1953 as a control for another child, had shown an identical normal pattern (Table V, page 18).

At the beginning of April 1954 he was discharged from hospital in as good a state of health as he had enjoyed since his illness began. When free of oedema he weighed 27·2 lb. (12·3 kg.), which is the lowest weight recorded for him. His height at the same time was 35 in. (89 cm.); as he was then four years old, there was already evidence of growth retardation. On May 6 he was again admitted with carpopedal spasm, and some oedema had reaccumulated. The serum-calcium level was 7·9 mg. per 100 ml., and the tetany passed off without treatment. It recurred four days later, and the pain was so severe that the child cried with it. Intravenous calcium gluconate relieved the spasm at once. During this admission a short-term calcium and phosphorus balance study was made. The results (Table II), although liable to error because of the short duration of study, indicated a negative daily calcium balance of 60 mg. The apparent failure of calcium absorption from the bowel, and the negligible (8 mg. per day) calcium excretion in the urine, are characteristic of the abnormal calcium metabolism demonstrated by Emerson and Beckman (1945) in young patients with nephrosis. On June 2 aminoacid chromatography of the urine was repeated, and revealed a grossly abnormal pattern with a greatly increased output of aminoacids. Details are shown in Table V (page 18). Thus, at some time between March 2 and June 2, the child had developed gross aminoaciduria and, like the earlier developing glycosuria, it persisted (Table V). It was also noticed for the first time during this occasion in hospital that the liver and spleen were

enlarged. The hepatomegaly was not great, but the spleen was palpable two finger-breadths below the costal margin, and it has subsequently remained at this size.

By the end of June the boy had spent 16 of the past 24 months in hospital and, because of the serious emotional effects of separation from his family, it was decided that he should go home. He was discharged with a serum-calcium level of 5·8 mg. per 100 ml. and serum-proteins 3·6 gm. per 100 ml. (albumin 1·7 gm., globulin 1·9 gm.). He was receiving calcium lactate and vitamin D, with instructions that he should be given as much milk as possible. Between

TABLE II

Calcium and Phosphorus Balances (May, 1954)

	Calcium	*Phosphorus*
Dietary intake (gm.)	2·175	3·239
Faecal output (gm.)	2·439	1·818
Urinary output (gm.)	0·036	0·917
Balance (5 days) (gm.)	−0·300	+0·504
	(−60 mg./day)	(+101 mg./day)

Collection for 5 days followed a preliminary period of equilibration.
The low daily intake of calcium was determined by the child's very poor appetite.

June and October he was brought to the out-patient clinic on five occasions with apparent tetany; each attack was treated symptomatically by the resident staff, and the child was returned home without blood examination. It was at this time difficult to assess his symptoms, as he obviously used them to gain attention and avoid unpleasant situations. Some of the 'tetanic' attacks may have been psychogenic (see below), but on October 10 he was again admitted to hospital with an entirely different clinical picture. He had been 'off-colour' for about three days, and complained of being very tired. His muscles were found to be extremely hypotonic, and he could not sit up in bed or even lift his head from the pillow. He was rather drowsy and confused. A clinical diagnosis of hypokalaemic paresis was made, and substantiated by the finding of a serum-potassium level of 2·7 mEq. per litre. He was given potassium chloride by mouth, and within 24 hours he had regained almost full muscle power, and was alert and lively. From this time blood examination was carried out fairly frequently. There was a persisting acidosis, a high level of blood-urea, serum-calcium normal for the plasma-protein level, and a rather low level of serum inorganic phosphorus (Fig. 1). With the oral potassium salt the serum-potassium remained at a high level. Gross aminoaciduria was still apparent, but no cystine deposit was present on examination of the cornea (Dr. A. Stanworth).

After the child's discharge on November 12, the intake of vitamin D was increased on account of a tendency for the serum-calcium to decrease and a constantly negative Sulkowitch test. An initial dose of 50,000 units of calciferol was soon increased to 100,000 units daily, and he has continued this dose to the time of writing. During the next four months he was brought to hospital with apparent tetany on six occasions; the attacks were all relieved by intravenous calcium gluconate, but the serum-calcium levels remained at low normal values, and it was thought that some of the attacks were not of metabolic but of psychological origin. This seemed to be substantiated after his next admission to hospital, when several attacks were terminated by the ward sister by a few sharp words, without any medication. The mother, however, thought that some of his attacks were brought on by the potassium chloride mixture, and about the

end of December she admitted that she had been giving it only infrequently. The resulting pronounced fall in the serum-potassium level is shown clearly in Fig. 1. In spite of the gross metabolic disorder it was hoped to continue supervision of the child as an out-patient, and admission to an open-air day school was arranged. On March 14, 1955, however, he had again to be admitted to hospital because of abdominal pain, vomiting, and a recurrence of his 'tetany'. The opportunity was taken to perform more detailed investigations than had hitherto been possible, and these are reported below.

At the time of admission the child was greatly undersized; he weighed 29 lb. 12 oz. (13·5 kg.), and was still only 35 in. (89 cm.) in height. Plate 1, Fig. 5 shows a normal child of the same age beside the patient, and demonstrates the marked stunting of growth. Bone development was also severely retarded; in Plate 1, Fig. 6 the X-ray appearances of Bobby's wrist and fingers are compared with those of a child of approximately the same height but two years younger. There is marked delay in the appearance of carpal centres, which correspond to a bone age of about two years, the age at which his disease started. In addition the bone cortex is thin, giving an appearance of 'osteoporosis' similar to that described by Emerson and Beckman (1945) in other nephrotic children. There is no radiological evidence of either the rickets or the osteitis fibrosa of classical renal osteodystrophy. Mentally the child was bright and intelligent, but showed the obvious psychological stigmata of his prolonged illness.

Renal and Metabolic Investigations (1955)

Because of the child's capricious appetite a strict metabolic balance study was not feasible, nor was it possible to enforce a diet of high protein and low sodium content. Accurate daily urine collections were made, but faeces were not collected, and the electrolyte intake was calculated from the food tables (McCance and Widdowson, 1946). The diet taken for the first 29 days of observation contained 28 mEq. K per day, and had a high salt content (≡68 mM. NaCl); subsequently it proved possible to get the patient to eat a diet containing the same amount of potassium but less salt (22 to 28 mM. NaCl; see Fig. 2). After a week without treatment potassium citrate was given by mouth; the dose was increased from 1·5 to 6·0 gm. (14 to 56 mEq. K) during a period of four days, and the latter dose was continued during the child's stay in hospital. When it was apparent that no further clinical effects could be expected from the administration of potassium alone, the salt content of the diet was reduced (*vide supra*), and cortisone therapy was started a week later. The dosage of cortisone and the changes in plasma and urinary electrolytes are shown in Fig. 2.

Laboratory methods. Sodium and potassium were determined by flame photometer; chloride in urine by potentiometric titration (Sanderson, 1952), and in serum iodometrically (Hawk, Oser, and Summerson, 1947); serum-phosphorus by a modification of King's method (1946); urinary phosphate by the method of Fiske and Subbarow (1925); plasma- and urine-urea by microdiffusion analysis (Conway, 1950); creatinine by the method of Bonsnes and Taussky (1945); and urinary reducing substance by the method of Shannon and Fisher (1938). Urinary total nitrogen was determined by Kjeldahl digestion and Nesslerization; urinary protein-nitrogen by trichloracetic acid precipitation with subsequent digestion of the precipitate. The daily output of amino-nitrogen was measured by an electrometric modification of the formol titration. Aminoacid

chromatography and quantitative measurement of the urinary output of individual aminoacids were done by Mr. T. Clarkson, using the method of Clarkson and Kench (1956). The total osmolarity of urine specimens was determined by the vapour-pressure method of Baldes and Johnson (1939). Exchangeable body potassium (K^e) was calculated from the 24-hour distribution of a dose of ^{42}K injected intravenously; three urine specimens were used for determination of specific activity, and appropriate correction was made for tracer excreted during the 24 hours of equilibration. Thiocyanate space was measured by conventional techniques.

Results (Tables III to VI; Figs. 2 and 3)

1. *Routine biochemical investigation.* Blood examination revealed the characteristic hypoproteinaemia and hypercholesterolaemia of the nephrotic syndrome (Table III). The serum was milky, and it has remained so during subsequent observations; a single determination of total fatty acids in the serum gave a value of 1,875 mg. per 100 ml. Filter-paper electrophoresis of the serum showed the changes typical of the nephrotic syndrome (Squire, 1953); γ-globulin was almost completely absent. This plasma-protein pattern remained essentially unchanged during therapy with potassium citrate and cortisone. Proteinuria, glycosuria, and aminoaciduria were constantly present.

2. *Total exchangeable body-potassium* (K^e). At the start of observations (March 22) K^e was 416 mEq., or 29·3 mEq. per kg. body-weight. This is well outside the range of 32 to 47 (mean 39) mEq. per kg. found by Gribetz, Corsa, Cook, Keitel, and Talbot (1954) in normal children; but, when related either to the patient's height or to the daily creatinine output, it fell close to the lower limit of the normal established by the same authors. The patient was free of apparent oedema when K^e was measured, but his body-weight was 1·1 kg. more than the 13·1 kg. found after the diuresis induced by cortisone (Fig. 2). If the latter figure is taken as the 'oedema-free body-weight', the corrected figure for K^e would be 32 mEq. per kg. oedema-free body-weight. The thiocyanate space on March 22 was 5,480 ml.

3. *Potassium 'balance' on the child's ordinary diet.* The diet taken was the utmost that the child could be coaxed to eat, and it was obvious that inadequate intake may have contributed to the production of potassium deficiency. Renal wastage of potassium was also of undoubted importance. The urinary output of potassium during the control week averaged 35 mEq. per day, and the serum-potassium level varied between 2·3 and 2·4 mEq. per litre. Neglecting entirely any faecal loss of potassium, the calculated minimal negative balance of potassium was 7 mEq. per day. Thus, despite hypokalaemia and potassium depletion, the daily urinary output was equivalent to 8·4 per cent. of the calculated total exchangeable body-potassium; and about 1·7 per cent. of the potassium store was being lost each day.

4. *Clinical and metabolic effects of potassium citrate.* Administration of potassium produced a definite improvement in appetite, and within a few days little food was rejected. It was also followed by a slight but definite diuresis (Fig. 3) and a considerable increase in the urinary output of sodium chloride (Fig. 2).

The mean daily urine volume during the four days before starting potassium therapy was 1,100 ml.; it increased to reach a mean of 1,300 ml. during the sixth to tenth days of treatment. In spite of the increased flow of urine and the

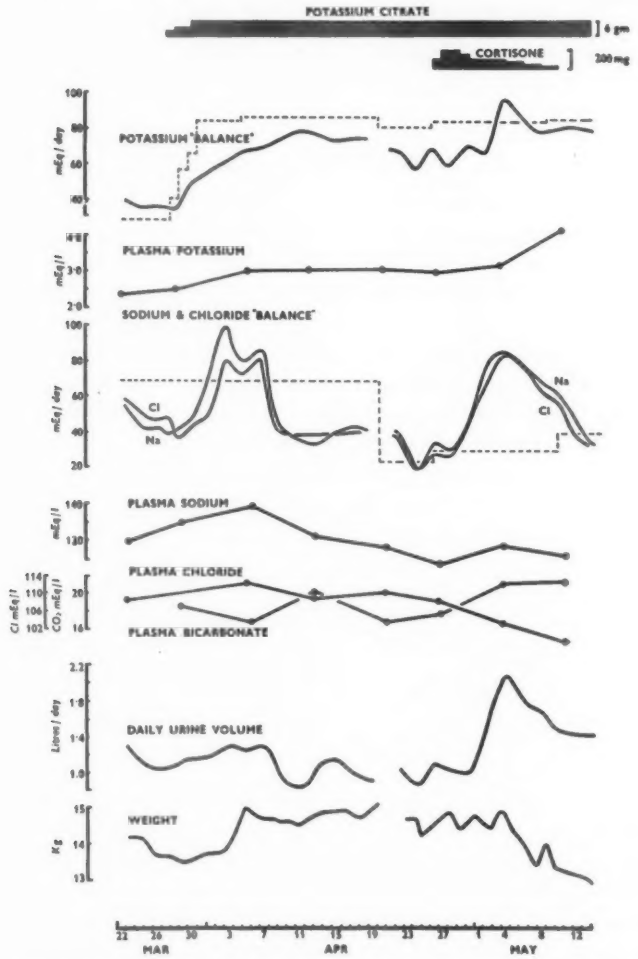

FIG. 2. Changes in plasma levels and urinary output of electrolytes following the administration of potassium citrate and of cortisone.

Continuous lines indicate the daily electrolyte output, and interrupted lines the calculated intake in the diet. The area between these two lines gives a crude index of the external electrolyte balance. The absence of data for faecal output and the errors involved in calculating intake limit the value of the 'balance' figures.

proportionately much greater increase in sodium output, the child became more oedematous, and the weight increased (Fig. 2). Potassium administration did not provoke tetany, which was not seen during this period in hospital. Potas-

sium output in the urine increased when the intake was augmented by administration of potassium citrate; after 10 days on the 6 gm. dose, the urinary output of 75 mEq. was within 10 mEq. of the calculated daily intake (85 mEq.; see Fig. 2). The patient then appeared to be in external potassium balance, but the serum-potassium level was no more than 3 mEq. per litre, and it did not exceed this value until after cortisone therapy. Although its precise magnitude could not be measured, there can be no doubt that we had produced a significant retention of potassium that was mainly accommodated within tissue-cells. It was presumably a simultaneous extrusion of sodium from cells that was responsible for the sodium diuresis (Fig. 2). The increased excretion of sodium was associated with a significant rise in the plasma-sodium level (Fig. 2) and an approximately 8 per cent. increase in the rate of creatinine excretion. The output of sodium and chloride was approximately doubled but, because of the high dietary intake of salt, the net negative balance was small, and most of the sodium extruded from cells was retained in the extracellular fluid. Determination of thiocyanate space on April 20 gave a value of 6,770 ml., an increase of 1,290 ml. on the figure obtained on March 22. Such expansion of apparent extracellular fluid volume would account for the development of oedema; and the gain of weight presumably reflected retention of water with the net increase in total body-cation. It is worth noting that the sodium diuresis stopped as soon as the patient came into apparent equilibrium with his intake of potassium (Fig. 2), an observation that again suggests a dependence of the sodium diuresis on retention of potassium. Administration of potassium citrate was followed by a significant fall in the plasma-urea level (Table III). Part of this fall may be ascribed to the increased body-water; but there was a significant increase in the urinary output of total nitrogen, and a 50 per cent. increase in the 24-hour urea clearance (Table III). As may be seen from Fig. 3A, the increased urine flow that followed the start of potassium therapy had the characteristics of an osmotic diuresis, in so far as it was associated with a significant increase in both the urinary output and concentrations of sodium and potassium. There was also an *increase* in the urine concentration of urea (Fig. 3A), rather than the decrease that is to be expected with an osmotic diuresis initiated by increased output of sodium and potassium. The kidneys were thus able to double the rate of total solute excretion with no more than a 20 per cent. increase in the rate of urine flow. This suggests that, as well as promoting a saline diuresis, potassium repletion may have facilitated the renal conservation of water (see below).

5. *Clinical and metabolic effects of cortisone.* An increase in the output of urine and of sodium and chloride was apparent by the fourth day of cortisone therapy. Thereafter the output of both water and salt increased, until on both the eighth and ninth days the volume of urine exceeded two litres. With this diuresis there was a significant reduction in weight (Fig. 2) and, when the child left hospital 18 days after starting treatment with cortisone, he was completely free of oedema. The diuresis induced by cortisone was associated with increased creatinine output, and with a significant increase in the 24-hour renal clearances of creatinine and urea (Table III). It was more protracted than the earlier

diuresis and, because of the lesser salt intake, it produced a gross negative balance of sodium and chloride (Fig. 2). The patterns of diuresis on the two occasions are compared in Fig. 3 (A and B). Whereas the diuresis induced by potassium was associated with increased urinary osmolarity and water con-

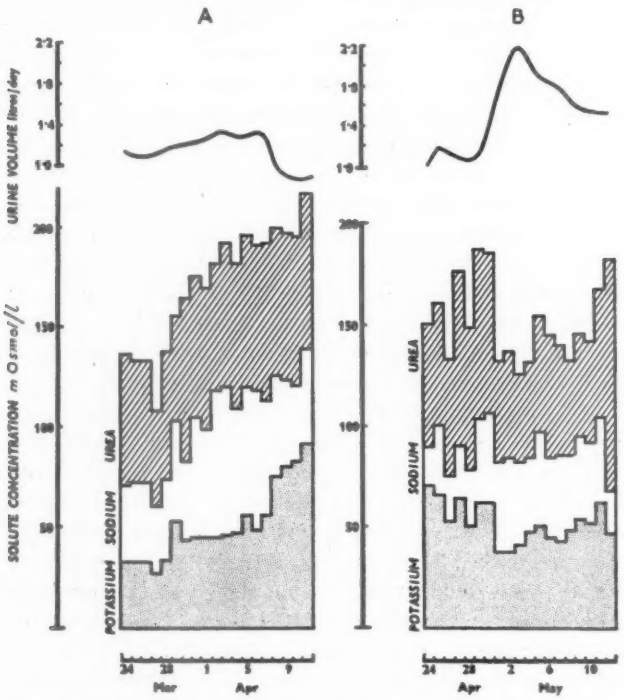

FIG. 3. The contrasting patterns of the diuresis induced by potassium citrate (*A*) and the diuresis following cortisone therapy (*B*).

The increase in urinary flow following potassium citrate administration was small (*A*), but there was an increase in both the excretion rate *and concentration* of potassium, sodium, and urea; the total osmolarity of the urine increased. The pattern was that of an osmotic diuresis apparently associated with improved water conservation (see text).

Cortisone produced a great increase in urinary flow and increased sodium chloride output (*B*); the urinary concentrations of potassium and urea fell. The pattern was that of a hypotonic saline diuresis. (Unfortunately, urinary total osmolarity was not measured.)

servation (as indicated by the gain of weight), cortisone facilitated the excretion of water as well as salt.

6. *Particular aspects of renal function.* (1) *Glomerular filtration.* It was not felt justifiable to subject the child to determination of inulin clearance, but the consistently elevated plasma levels of creatinine and urea, and the low C_{urea} and C_{cr} (Table III) indicated a considerable reduction in glomerular filtration rate. Both potassium citrate and cortisone increased the filtration rate, and each

increase was accompanied by an augmented output of protein, glucose, and aminoacids.

(2) *Polyuria-polydipsia; urinary osmolarity.* The child's excessive drinking was often remarked by the nursing staff. Before potassium replacement was started the daily volume of urine was between 1·0 and 1·3 litres; later, after the first saline diuresis and when there was clinically obvious oedema, the daily output of urine remained at about 1 litre. This output is excessive even for a

TABLE III

Blood Changes and Renal Clearances During Potassium Citrate and Cortisone Therapy

	Serum												
Date, 1955	*Na (mEq./l.)*	*K (mEq./l.)*	*Cl (mEq./l.)*	*CO_2 (mEq./l.)*	*Inorganic P (mg./100 ml.)*	*Albumin (gm./100 ml.)*	*Globulin (gm./100 ml.)*	*Cholesterol (mg./100 ml.)*	*Plasma-urea (mg./100 ml.)*	*Plasma-creatinine (mg./100 ml.)*	*C_{urea} (ml./min.)*	*C_{cr} (ml./min.)*	*C_K (ml./min.)*	*C_P (ml./min.)*
March 22	130	2·34	109	18	3·2	..	..	480	56	..	5·2	..	11·9	7·4
March 28	136	2·40	..	18·9	2·7	..	..	..	..	..	..	..	9·3	5·6
Potassium citrate therapy started March 28, 1955														
April 5	140	2·95	113·5	17	2·7	1·1	3·1	480	47	..	7·8	..	15·5	6·1
April 12	132	3·0	110	20·4	3·6	..	..	..	44	1·85	6·5	9·5	18	5·6
April 20	129	3·0	111	17·2	3·46	..	..	..	..	..	..	..	18	5·8
April 26	129	2·95	109	18·1	..	0·9	2·7	610	41	1·79	6·9	8·8	16	..
Cortisone therapy started April 26, 1955														
May 3	130	3·15	104	21·6	..	1·2	2·3	640	45	1·29	8·4	13	15·9	..
May 10	127	4·15	98	21·9	..	1·8	3·0	590	43	1·32	7·5	10	13·4	..
Discharged from hospital May 14, 1955														
May 28	128	4·1	106	18·6	..	0·8	3·3	360	..	..	..	..	..	..

The values C_{urea}, C_{cr}, C_K, and C_P refer to the renal clearances of urea, creatinine, potassium, and phosphate; they were calculated from the appropriate 24-hour output and plasma levels.

The presence of lipaemia may have produced falsely low values for serum-sodium and -chloride (Albrink, Hald, Man, and Peters, 1955); the influence of this factor on the serum levels of potassium would be very small, and correction would not bring the potassium values to normal.

The serum alkaline phosphatase level was always normal.

normal child of his age, but it is conspicuously unusual in a nephrotic child with oedema. In nephrotic children between the ages of four and six years, Passaro (1954) recorded daily volumes of urine of 130 to 500 ml. The problem is to decide whether, in Bobby, polydipsia or polyuria was primary. During the week before commencement of potassium citrate therapy the mean total-osmolarity of the 24-hour urine specimens was 280 mOsmols per litre, and the range 220 to 315 mOsmols per litre. Unfortunately, at this time, no test of renal concentrating capacity was made by fluid deprivation or vasopressin administration. During the nine days of the first diuresis the mean urinary osmolarity was 360 mOsmols and the range 325 to 385 mOsmols per litre. On completion of this saline diuresis the urinary flow fell significantly, and the urine became still further concentrated (Fig. 3A); during the subsequent nine days osmolarity of the 24-hour specimens ranged from 330 to 440 mOsmols per litre, with a mean value of 385 mOsmols per litre. In the absence of a concentration test during the control week, one cannot certainly exclude primary polydipsia as cause for the dilute urine produced at that time; but the measured intake of fluid actually

increased when the child was given potassium citrate, and at that time the osmolarity of the urine increased in spite of this augmented intake of water. This suggests that the polyuria was due to hyposthenuria, and that potassium replacement had increased the renal osmolar concentrating capacity. On a later

TABLE IV

Nitrogen Partition in the Urine

	(Urea+NH_3)N	*Protein-N*	*'NH_3-N'*
Before therapy with cortisone (25 determinations) . . .	44% (40–47)	37·5% (30–43)	10·5% (8–13)
During therapy with cortisone (14 determinations) . . .	50% (41–58)	32% (29–43)	15% (11–19)

The mean value and range of each variable is recorded.

The low urea-N and high protein-N are characteristic of the nephrotic syndrome; ammonia output was negligible. The very high NH_3-N coefficients were obtained by formol titration. A single value for the NH_3-N coefficient, in which the NH_3-N was determined by a more specific method, is included in Table VI.

TABLE V

The Evolution of Aminoaciduria

Aminoacid	*Date* *May 4, 1953*	*June 2, 1954*	*October 11, 1954*	*March 4, 1955*
Cysteic acid (from cystine) . . .	..	6	6	2
Aspartic acid	..	5	2	..
Glutamic acid	..	7	3	3
Serine	5	..	5	3
Glycine	6	8	7	5
Threonine	..	6	..	2
Alanine	5	10	8	6
Tyrosine	..	5	2	..
α-amino-*n*-butyric acid	..	5	..	..
Valine	..	9	5	6
Leucine	..	9	5	6
Citrulline	..	6	6	..
Glutamine	..	10	8	7
Proline	..	+	..	..
Histidine	..	5	2	..

A chromatogram run on March 2, 1954 was identical in pattern with that of May 4, 1953, but quantitative figures were not recorded. At that time the renal glycosuria was already established.

The above determinations were done by Miss V. K. Wilson, using deproteinized urine containing 250 μg. N. Chromatography (18×22 in.) in phenol followed by tetrahydrofurfural; colour development with 0·1 per cent. ninhydrin. The figures represent intensity of ninhydrin colours in arbitrary units (Dent, 1947).

occasion, when the patient was probably again somewhat depleted of potassium, administration of 2 units of pitressin tannate produced urine with osmolarity no higher than 310 mOsmols per litre.

(3) *Capacity for urine acidification.* Since the plasma-bicarbonate was consistently subnormal (total CO_2 17 to 18·9 mEq. per litre), no acidifying load of ammonium chloride was given. When the plasma-CO_2 was 18 mEq. per litre the pH of urine collected under oil was 6·8; the daily excretion of bicarbonate was 5 to 6 mEq., and ammonia output did not exceed 5 mEq. per diem. This

represents an impaired capacity for urine acidification and an inadequate ammonia output in the presence of a metabolic acidosis. The extracellular acidosis was not corrected by administration of potassium citrate. A significant elevation of plasma-bicarbonate followed the cortisone-induced diuresis (Table III).

(4) *Glycosuria.* Before treatment the excretion of reducing substance in the urine varied between 0·6 and 1·0 gm. per diem. It increased to about 1·4 gm.

TABLE VI

Quantitative Assay of Urinary Amino-nitrogen

The control data are from 12 normal adult men (Clarkson and Kench, 1956).

	Amino-nitrogen mg./litre Bobby J.†	*Amino-nitrogen mg./gm. creatinine Adult male subjects (mean and standard deviation)*	
Glutamic acid	0·8	1·6	(0·9)
Lysine	1·6	2·0	(1·2)
Glutamine	38·0	7·0	(3·4)
Asparagine	5·0	0·9	(1·6)
Histidine	3·5	5·2	(2·3)
Glycine	16·6	16·5	(5·1)
Alanine*	38·2	6·4	(1·1)
Serine	10·8	4·2	(1·1)
Proline	4·1	0·3	..
Tyrosine	3·7	1·5	(0·7)
Valine	12·6	1·0	(0·4)
Leucine and isoleucine	19·8	0·9	(1·0)
Threonine	9·1	1·7	(0·9)
Tryptophane	0·7	0·6	(0·5)
Total	164·5	52·0	(10·5)

* Uncorrected for the presence of β-aminoisobutyric acid.

† These measurements were made on a 24-hour specimen of urine containing 240 mg. creatinine and 4·64 gm. total nitrogen in a volume of 1,080 ml. The daily output of amino-acids greatly exceeded that of the normal adults, whose daily output of creatinine is near to 1 gm.

The above determinations were made by Mr. T. W. Clarkson, using the quantitative method of Clarkson and Kench (1956). Data obtained from normal children by this method are not available for comparison; the adult figures are close to those obtained by Stein (1953) using ion-exchange column chromatography. The patient's aminoacid excretion may be compared with the quantitative data obtained by Dustin, Moore, and Bigwood (1955) in a study of the 'physiological' aminoaciduria of mature and premature infants. In the patient, the NH_2-N coefficient of 3·8 per cent. is close to the values found by these authors in prematurity.

during the first diuresis, and up to 1·6 gm. per diem during cortisone-induced diuresis. Change of output correlated fairly well with change of creatinine output.

(5) *Proteinuria; nitrogen partition in urine; aminoaciduria.* Protein output varied between 6 gm. and 16 gm. per diem, increasing usually with increase of urine flow. It was not significantly influenced by cortisone therapy. The nitrogen partition in the urine is shown in Table IV. The low urea-nitrogen and high protein-nitrogen values are characteristic of the nephrotic syndrome; and the high level of amino-nitrogen indicates a gross aminoaciduria. The very high amino-nitrogen coefficients were obtained by formol titration, and the values

were remarkably constant. The daily output of amino-nitrogen by this method varied between 350 and 600 mg., increasing to reach values of 700 to 900 mg. during the diuresis induced by cortisone. Details of the daily output of individual aminoacids, together with normal data derived by similar techniques, are shown in Table VI. The results of earlier chromatographic studies are shown in Table V. The excretory pattern was not appreciably influenced by either potassium or cortisone administration.

(6) *Renal 'handling' of potassium.* The continued excretion of potassium in the urine, despite hypokalaemia and potassium depletion, place the kidney disorder in the category of 'potassium-losing renal disease'. Values for 24-hour potassium clearances are shown in Table III, where it can be seen that they were invariably higher than the urea and creatinine clearances. Urea clearance is an unreliable index of glomerular filtration rate in the nephrotic syndrome, and endogenous creatinine clearance tends to overestimate glomerular filtration to an unpredictable extent (Barnett, Forman, and Lauson, 1952); but the very considerable margin by which potassium clearance exceeded that of creatinine makes it highly probable that potassium was being cleared at a rate greater than glomerular filtration. The potassium clearance values of about 10 ml. per minute before starting therapy with potassium citrate fall within the customary range for normal plasma levels; but with potassium levels as low as 2·4 mEq. per litre the normal kidney would conserve potassium to the fullest extent, and lower clearance values are to be expected (Mahler and Stanbury, 1956). With potassium therapy the clearance values increased without much change in serum-potassium levels and, although the clearance of creatinine increased, it remained below the potassium clearance. Cortisone at first produced no change in potassium clearance; but the peak of diuresis was associated with a short-lived increase in potassium output, and the potassium clearance then reached a value of 21 ml. per minute. Towards the end of the diuresis produced by cortisone, the plasma-potassium increased significantly without a corresponding increase in urinary excretion; in consequence the potassium clearance fell, and its value with a plasma level of 4·1 mEq. per litre was lower than it had previously been at 3 mEq. per litre.

(7) *The renal excretion of calcium and phosphate.* The urinary excretion of phosphorus varied between 250 and 200 mg. per day. There was a transient drop in the excretion rate (to 185 mg. per day) during the first three days of potassium citrate therapy and, despite a reduction in the level of serum-phosphate, the calculated 24-hour renal clearance of phosphate fell (see Table III). Calcium excretion varied fairly widely, but the average daily output in the urine was close to 50 mg. This suggests that calciferol therapy had increased the absorption of calcium from the bowel (compare the urinary excretion rate in 1954, Table II).

Discussion

The clinical picture. In a patient exhibiting so many atypical features, it might be doubted whether the case should be classified as what is variously

designated 'lipoid nephrosis', 'the nephrotic syndrome', or 'Type 2 nephritis' (Ellis, 1942). The onset with massive oedema (Plate 1, Fig. 4) and proteinuria; the hypoproteinaemia, plasma electrophoretic pattern, and lipaemia; the normal blood-pressure; and the initially normal blood-urea, were all typical of the nephrotic syndrome. Moreover, from the routine testing of urine for glucose, and the fortuitous aminoacid chromatogram run in the 10th month of the child's illness, it is established that glycosuria and aminoaciduria formed no part of the original disease picture. This is a point of considerable importance, for the fully developed clinical picture—with polyuria, glycosuria, aminoaciduria, metabolic acidosis, potassium depletion, dwarfism, demineralization of the skeleton, and hepato-splenomegaly—closely resembles that of the Lignac-Fanconi syndrome or 'cystine storage disease' (Bickel, Smallwood, Smellie, and Hickmans, 1952). It is unfortunate that Tegelaers and Tiddens (1955) used the term 'nephrotic-glucosuric-aminoaciduric dwarfism' in describing their two patients, for essentially the same appellation has been attached to cystine storage disease (Fanconi, 1936). The two syndromes are undoubtedly distinct, and the best evidence for this is the absence at autopsy of cystine storage in the patient of Tegelaers and Tiddens (1955). Less conclusive is the absence of cystine deposits in the corneae and conjunctivae of our own patient.

The various unusual features which collectively make the present patient something of a clinical curiosity have, however, all occurred in other children with the nephrotic syndrome. A generalized reduction of the radiological density of the bones of young nephrotic patients was described by Emerson and Beckman (1945), who thought that its degree varied with the severity of the primary disease. Other cases have been described by Gottfried, Steinman, and Kramer (1947), Gaburro, Baggio, and Ferrante (1952), and Durand and de Toni (1953). The skeletal disorder has been classified as 'osteoporosis', and this is probably a correct interpretation of the radiological findings, but histological confirmation is lacking. The absence of radiologically apparent rickets (as in our own patient; Plate 1, Fig. 6) and the normal serum levels of alkaline phosphatase, phosphate, and ionic calcium accord better with an underlying bone atrophy or porosis than with osteomalacia. The extreme protein depletion of the nephrotic child is likely to limit the availability of aminoacid precursors essential for bone matrix formation, and this could lead to reduction of the skeletal mass in a manner analogous to the production of osteoporosis in other circumstances (Albright and Reifenstein, 1948). Protein deficiency may also account for the retardation of growth that was so conspicuous in our own patient (Plate 1, Fig. 5) and those of Tegelaers and Tiddens (1955). An alternative possibility is that chronic depletion of potassium interfered with growth in these three patients; the potassium-deficient animal does not grow, and potassium-depleted man has an impaired capacity for protein synthesis (Mahler and Stanbury, 1956; Frost and Smith, 1953). It is appreciated that some degree of dwarfism may be expected with any serious renal disease, but we personally tend to associate it with a greater degree of renal excretory failure than was present in these three patients.

Hypocalcaemia in the nephrotic syndrome can usually be ascribed to the hypoproteinaemia (Salvesen and Linder, 1923–4) and, since the plasma level of ionic calcium remains normal (Liu, 1926–7), clinical tetany is extremely rare (Metcoff, Rance, Kelsey, Nakasone, and Janeway, 1952). The hypocalcaemic tetany described as complicating nephrosis by Klinke (1929), Gaburro, Baggio, and Ferrante (1952), and Imperato (1953), developed in association with nitrogen retention and high levels of serum inorganic phosphorus. In Bobby, and in the two patients of Tegelaers and Tiddens (1955), tetany developed in company with low or normal phosphate levels. The depression of the serum level of calcium in our own patient was at times proportionately greater than the diminution of the serum-proteins. It is therefore almost certain that the ionized fraction of the serum-calcium was significantly reduced; and the immediate clinical response of the tetany to parenterally injected calcium salts tends to support this contention. Why this disproportionate reduction of the serum-calcium should have developed is less certain, but it is known that the prolonged administration of cation exchange resins can give rise both to hypocalcaemia (Greenman, Shaler, and Danowski, 1953) and to tetany (Dock and Frank, 1950). Children with nephrosis absorb little or no calcium from the bowel, and the output of calcium in the urine is negligible (Emerson and Beckman, 1945); this abnormality was shown to be present in our own patient. In patients with this metabolic abnormality cation exchange resins are likely to increase the negative calcium balance by increasing the loss of calcium in the faeces, and the possibility of compensating this effect by reducing the urinary output of calcium does not exist.

Tetany may also develop as a complication of potassium depletion (Strong, 1951; Roussak, 1952; Fourman, 1954; Fourman and McCance, 1955). Since each of the three patients under discussion was apparently depleted of potassium, the question arises as to whether this was responsible for the tetany. In our own patient we think it unlikely, since the hypocalcaemia accounted adequately for it, and since hypokalaemic tetany is not relieved by the injection of calcium salts. Moreover, it seems probable that the metabolic alkalosis commonly associated with potassium depletion is more significant for the production of tetany than the potassium deficiency itself (Stanbury and Mahler, to be published), and all three patients had a marked metabolic acidosis. Other aspects of the problem of potassium deficiency in nephrosis are discussed separately below.

We can offer no satisfactory explanation for the enlarged spleen that was present in our patient; but, even though this too remains unexplained, some degree of hepatomegaly is seen in a significant proportion of nephrotic children (Gottfried, Steinman, and Kramer, 1947; Barnett, Forman, and Lauson, 1952). In thus discussing the main symptoms of the present patient, it has been our intention to emphasize the fact that he is by no means unique. On clinical grounds there is not sufficient evidence to distinguish his illness as something different from the commonplace nephrosis of childhood. His miscellaneous metabolic and biochemical abnormalities have also been seen, separately or collectively, in other nephrotic patients.

The renal tubular disturbance: its evolution and possible aetiology. Aminoaciduria and glycosuria may occur more often in the nephrotic syndrome than is generally realized. In adults, however, they must be uncommon. Among some 30 patients in the Department of Experimental Pathology, University of Birmingham, only two were found to have renal glycosuria and aminoaciduria (Dr. J. D. Blainey, personal communication). In 40 adults and adolescents whose condition was classified as Type 2 nephritis, observed over a period of eight years in the Manchester University Department of Medicine, none has been known to develop glycosuria (Dr. M. H. Roscoe, personal communication), but aminoaciduria has not been specifically sought. On the other hand, an occasional nephrotic child attending the Royal Manchester Children's Hospital has been found to have glycosuria (Miss V. K. Wilson, personal communication). Bickel and Souchon (1955) examined 15 nephrotic patients over a course of five years, and in only five of them was there 'eine leichte oder mässige' aminoaciduria: in three of these five patients the aminoaciduria developed coincidentally with the taking of a diet rich in protein. Durand and de Toni (1953) made chromatographic studies of the urine of 10 nephrotic children, and concluded that aminoacids were present in greater number and quantity than in normal subjects. Imperato (1953) arrived at a similar conclusion, and his results are made more impressive by the inclusion of normal data. By the chromatographic method used, the urine of normal children between the ages of two and 12 years was found to contain small quantities of glutamic acid, β-aminoisobutyric acid, alanine, glycine, histidine, lysine, serine, and taurine. In each of five nephrotic children the output of these aminoacids was considerably increased, and urine from the five patients contained collectively an additional 11 aminoacids (valine, threonine, methionine, the leucines, tryptophane, arginine, cystine, tyrosine, proline, and citrulline). The aminoaciduria in the present patient was qualitatively similar (Tables V, VI); from its magnitude and from the chromatographic pattern, we have assumed that it resulted from defective tubular reabsorption of aminoacids. This has not been established by plasma aminoacid assay, but the presence of other disturbances of tubular function increases the probability that the supposition is correct. The aminoaciduria in our patient could not be related to a high intake of dietary protein, for when we obtained the data shown in Table VI he was eating little more than 0·5 gm. of protein per kg. of body-weight per day.

Since defective tubular function was not present early in the illness of our patient, it is of interest to relate its development to the general metabolic disturbance also present. This is attempted in Fig. 1 and Table VII. Lowering of the serum-sodium level and a developing metabolic acidosis are expected results of resin therapy (Spencer and Lloyd-Thomas, 1954; Fried and Sala, 1954); but prompt recovery of normal plasma-bicarbonate levels should follow withdrawal of treatment. One month after stopping resin treatment in the present patient the serum bicarbonate was no higher than 15 mEq. per litre (Fig. 1), and complete recovery did not occur subsequently. This sustained metabolic acidosis was not associated with phosphate retention or gross azotaemia, and it must be

ascribed to the demonstrated failure of tubular mechanisms concerned with urine acidification. The onset of this particular tubular abnormality cannot be precisely dated; it appeared to be established by the 13th month of illness. At the 13th month hypokalaemia was first detected, and this remained uncorrected for 15 months. Evidence that the hypokalaemia reflected significant potassium depletion is discussed below. Although high-normal levels of serum-potassium were recorded during the ninth to 11th months, there was then gross acidosis

TABLE VII

The Evolution of the Renal Disease

Metabolic or renal abnormality	*First detected*	*Subsequent course*
Low serum-sodium	3rd month	Present irregularly (Fig. 1)
ELEVATED BLOOD-UREA	9th month	Continued but variable (Fig. 1)
METABOLIC ACIDOSIS	9th month	PERMANENT
Hypokalaemia ($\leqslant$ 3 mEq./l)	13th month	Continued until 28th month; recurred 30th month
Disproportionate hypocalcaemia	20th month	Irregular
RENAL GLYCOSURIA	21st month	PERMANENT
AMINOACIDURIA	24th month	PERMANENT
HYPOSTHENURIA	Unknown	

Cation exchange resins were administered from the 2nd to 10th month.
Other therapy is shown in Fig. 1.

(serum bicarbonate 10 mEq. per litre) and some nitrogen retention (blood-urea about 60 mg. per 100 ml.); and with this combination of circumstances normal or high serum-potassium levels are compatible with potassium depletion (Moore, Edelman, Olney, James, Brooks, and Wilson, 1954). Acquired 'tubular acidosis' appears to be a rare complication of the nephrotic syndrome, whereas even moderate potassium depletion of short duration can impair the renal capacity for production of maximally acid urine (Clarke, Evans, MacIntyre, and Milne, 1955). This particular tubular defect in our patient may therefore be a result of potassium depletion induced by resin therapy, rather than a natural development of the primary disease. Sustained potassium deficiency, even in patients without primary renal disease, can produce a wide variety of functional renal defects, and histological changes that may proceed to necrosis of renal tubular cells (Schwartz and Relman, 1953; Relman and Schwartz, 1955; Mahler and Stanbury, 1956; Stanbury and Mahler, to be published). Among the recognized effects of potassium depletion is the development of polydipsia and polyuria due to hyposthenuria, which may persist for months after the potassium deficit has been made good (Relman and Schwartz, 1955). The occurrence of this syndrome in the present patient has been discussed in detail; it was also present in one of the two closely similar, potassium-depleted, nephrotic patients of Tegelaers and Tiddens (1955). Polyuria is so exceptionally rare a symptom in nephrotic patients that one more readily accepts some alternative cause for its development; unfortunately, we do not know when polyuria first commenced in our patient. Renal glycosuria developed when hypokalaemia, and presumably potassium deficiency, had been present for eight months; aminoaciduria followed shortly afterwards (Table VII). There was no evidence that potassium repletion

improved these tubular defects. In contrast, a rapidly reversible aminoaciduria has been described in potassium-depleted patients (Denton, Wynn, McDonald, and Simon, 1951) but so far this remains an isolated observation.

We do not intend the previous discussion to imply a personal belief that all the tubular disorders acquired by our patient are to be attributed to potassium deficiency. The two nephrotic patients of Blainey (1954) with renal glycosuria and aminoaciduria had no other tubular defects, no metabolic acidosis, and no potassium depletion (personal communication). It is likely that the development of aminoaciduria in the nephrotic syndrome will prove to be due to the grossly disordered protein metabolism, or even to the effects of renal tubular ischaemia (Allen, 1955). Potassium deficiency, as a state potentially damaging to the tubules, may be another factor in the development of such changes; it may also add to the effects of protein depletion by impairing protein synthesis (Mahler and Stanbury, 1956; Frost and Smith, 1953). That potassium depletion contributed materially to the production of the renal abnormalities in our patient we have no doubt; potassium replacement led to an increased rate of glomerular filtration, to a lowering of the blood-urea level, and probably to an improved renal capacity for osmolar concentration. Similar changes have followed replacement of potassium in the 'nephropathy of potassium deficiency'.

Potassium deficiency in the nephrotic syndrome. Opinion varies as to the frequency with which potassium deficiency develops in nephrosis. Low serum levels of potassium have been found in a proportion of patients by several authors (Passaro, 1954; Durand and De Toni, 1953); but Gribetz, Corsa, Cook, Keitel, and Talbot (1954) found the total exchangeable potassium to be no lower in nephrotics than in a group of normal children. An opinion that seems to be soundly based is that significant distortion of electrolyte metabolism is more likely to arise as a complication of treatment than as a spontaneous development (Barnett, Forman, and Lauson, 1952). Cation exchange resins have been shown to increase the faecal loss of potassium in nephrotic children (Mateer, Erhard, Price, Weigand, Peters, Danowski, Tarail, and Greenman, 1951). Their use in the treatment of adults with Type 2 nephritis has led to potassium deficiency (Spencer and Lloyd-Thomas, 1954), and in children to the production of hypokalaemia accompanied by severe muscular weakness (Passaro, 1955). Similar complications have followed therapy with corticotrophin, which leads to loss of potassium in the urine (Metcoff, Rance, Kelsey, Nakasone, and Janeway, 1952). Fox and Slobody (1951) analysed tissues obtained at autopsy from six nephrotic children who had died suddenly. As compared with control material, muscle from the nephrotic patients showed a gross reduction in potassium content and an increase in water, sodium, and chloride. The changes were similar in magnitude to those produced in animals experimentally depleted of potassium, or following prolonged treatment with alkalis or deoxycortone. If it can be agreed that agonal changes in tissue composition did not occur, their findings are impressive and of obvious significance. It must be remembered, however, that many of these nephrotic patients had been treated with large doses of alkaline sodium salts, following the therapeutic regimen of Fox and McCune (1948).

Consequently, in this group of patients also, it is not possible to exclude therapy as a cause of the apparent potassium depletion.

There can be no doubt that our own patient became severely depleted of potassium. This was shown by the hypokalaemia that was sustained in the presence of metabolic acidosis, by the low value of the exchangeable body-potassium, and by the clinical development of hypokalaemic muscular paresis. Further evidence of potassium deficiency was provided by the very considerable retention of potassium that followed its administration as citrate (Fig. 2). One can readily see, from the example of this patient, how a deficiency of potassium may arise in the course of a nephrotic illness. We have previously mentioned the child's poor appetite and the consequent low intake of potassium; difficulties of feeding appear to arise in most of these young patients (Barnett, Forman, and Lauson, 1952). The diet chosen by the child usually contained much sodium, and this was likely to increase the renal loss of potassium produced by the adrenal salt-retaining steroids (Seldin, Welt, and Cort, 1951; Howell and Davis, 1954). The combination of a poor diet with the therapeutic use of cation exchange resins was undoubtedly of first importance in producing potassium deficiency in our patient. In a group of adult patients receiving 60 gm. 'katonium' daily, and with a dietary potassium intake of 70 to 98 mEq., Spencer and Lloyd-Thomas (1954) found an average negative potassium balance of 80 mEq. per week. It may be recalled that Bobby received 30 gm. of 'katonium' for nearly a year and, although the dietary intake of potassium is not known, it is likely to have been insufficient to counter the potassium-depleting effects of the resin. During this period of treatment the blood-urea level began to rise (Fig. 1), and at the end of the year a metabolic acidosis and hypokalaemia were clearly established.

Nephrotic patients may also lose potassium in the urine. This undoubtedly occurs during therapy with corticotrophin or cortisone, and we have demonstrated its importance in maintaining and intensifying potassium deficiency in the present patient. It has been shown experimentally that the increased renal tubular reabsorption of sodium in the nephrotic syndrome is associated with a propensity to loss of potassium by the kidneys. A normal individual who receives an injection of sodium chloride, or the sodium salt of an unabsorbable anion such as *p*-aminohippurate or thiosulphate, responds by excreting the appropriate sodium salt in the urine. The nephrotic patient excretes the injected anion partly as the sodium and partly as the potassium salt; more potassium may be excreted than is simultaneously filtered by the glomeruli (Burnett, Burrows, and Commons, 1949; Metcoff and Wallace, 1950; Metcoff, Nakasone, and Rance, 1954). This pattern of renal behaviour is peculiarly relevant to the present patient, in whom the failure of aminoacid reabsorption led to the excretion of large amounts of 'unabsorbed anion'. Reckoned on the figures obtained by formol titration, there appear to be some 25 to 40 mEq. of aminoacid requiring excretion in company with cation; the figures for aminoacid excretion obtained by the method of Clarkson and Kench (1956) suggest that a smaller quantity may be more appropriate. In any event, this provides an obvious source of potassium wastage; combined with the potassium loss resulting from the patient's inability to

produce an acid urine, it will account for the difficulty experienced in effecting potassium repletion. Considered solely from the standpoint of disordered renal function, the present patient resembles very closely a previously reported case of the so-called 'adult Fanconi syndrome' (Milne, Stanbury, and Thomson, 1952). It is not known what role aldosterone may play in producing renal wastage of potassium in the nephrotic syndrome, but there is good evidence that its production is increased in such patients (Luetscher and Johnson, 1954; Luetscher, 1954; Luetscher, Neher and Wettstein, 1954; Axelrad, Cates, Johnson, and Luetscher, 1955). Administration of potassium citrate to our patient led to retention of potassium and a diuresis of sodium, but it did not restore the serum-potassium level to normal. Precisely similar effects have followed the administration of potassium salts to patients with primary aldosteronism (Conn, 1955*a*; Evans and Milne, 1954), and it was only after removal of the aldosterone-secreting tumour that the serum-potassium returned to normal (Conn, 1955*b*). It is consequently of interest that the serum-potassium level in our patient became normal only after therapy with cortisone (Fig. 2; Table III). The urinary output of aldosterone returns to normal values when the treatment of a nephrotic patient with cortisone is followed by a satisfactory diuresis (Luetscher, 1954).

General implications of the present observations. It must be admitted that the cause of aminoaciduria and glycosuria in our own and other nephrotic patients is not apparent. A similar pattern of renal tubular abnormality develops in cystine storage disease, where it is thought to result from the inherited disorder of aminoacid and protein metabolism (Baar and Bickel, 1952; Bickel, 1955; Bickel and Souchon, 1955). The clinical similarity between the fully developed Lignac-Fanconi syndrome and the condition of our own patient is impressive and suggestive. In each disease there is a fundamental disorder of nitrogen metabolism, and there may be a complicating potassium deficiency; potassium deficiency may further distort protein metabolism and itself contribute to the production of renal damage. The mutual interrelations of these various factors are by no means understood in either syndrome, and it would be unwise to take the comparison further. None the less, a carefully planned study of the evolution of renal tubular disturbance in nephrotic children could perhaps by analogy provide some insight into the causes of similar defects in the much rarer cystine storage disease. A further implication of our observations is of more immediate practical importance. One cannot tell, early in a nephrotic illness, whether the child will recover or not, but the distressing nature of the principal symptom compels the physician to use a variety of drastic methods in attempting its relief. Among the treatments that are or have been used for the relief of oedema, alkaline sodium salts, cortisone, corticotrophin, and cation exchange resins are all capable of producing potassium depletion. This fact is well recognized, as is the desirability of providing a supplement of potassium salts; but in actual practice it is often forgotten, as it was in this patient. Although the damaging effects of potassium deficiency on the kidney usually permit recovery, this may not be the case when the affected cells are already suffering a severe depletion of protein, and a long-maintained depletion of potassium may produce changes that are not

reversible. Symptomatic treatment must not be allowed to prejudice the chances of recovery.

The authors wish to express their gratitude to Sister McCormick (Diet Room Supervisor) and Sister Murney (Ward Sister), of the Duchess of York Hospital for Babies, for their careful help with the metabolic studies. Miss V. Baccus assisted with the biochemical work; and the determinations of plasma-proteins and electrophoresis were kindly done by Mr. M. Bell, of the Department of Clinical Pathology, Manchester Royal Infirmary.

Summary

A child is described who, when his illness began at the age of two years, had all the typical clinical and biochemical features of the nephrotic syndrome. During the following two and a half years he developed a variety of unusual complications, including severe hypocalcaemic tetany and a single episode of muscular paresis attributable to potassium deficiency. At the age of five years he was dwarfed, and his skeleton was porotic: in addition to massive proteinuria and hypoproteinaemia, he was found to have polyuria, glycosuria, gross aminoaciduria, potassium deficiency, and a metabolic acidosis, associated with the inability to produce urine of maximum acidity. Detailed studies were made of certain aspects of renal function, and of the metabolic effects of therapy with potassium citrate and cortisone.

Published records were found of two nephrotic patients who followed an apparently identical clinical course; other patients have had one or more of the unusual clinical and biochemical complications. It is concluded that the primary disease in our patient was classical 'nephrosis' or 'Type 2 nephritis'.

An attempt to ascertain the causes for the unusual course of the disease was only partly successful; but it was possible to trace the sequential development of the specific disorders of renal tubular function. The development of potassium deficiency, probably resulting from therapy with cation exchange resins, appeared to be related temporally to the development of the renal tubular abnormalities, but a causal relationship was not certainly established. Replacement of the potassium deficit was followed by improvement in certain renal functions.

It is pointed out that most forms of treatment used for the attempted relief of oedema are capable of inducing potassium deficiency. In this way symptomatic treatment may prejudice the chances of recovery from the renal disease.

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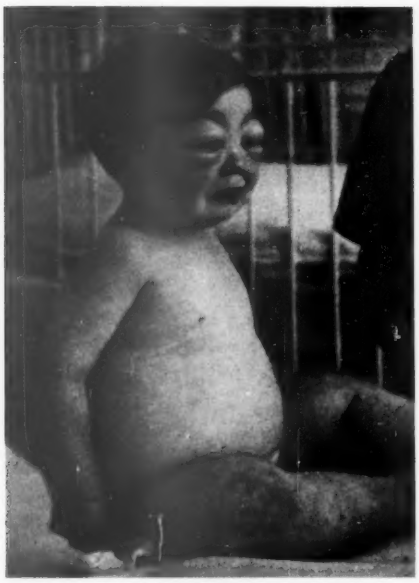

FIG. 4. The clinical appearance of the child in the second week of his illness (age, two years and four months). The anasarca is very obvious, and serves to emphasize the nephrotic nature of the disease at its beginning

FIG. 5. Dwarfism at the age of five years (March 1955). The patient is compared with a normal child of his own age

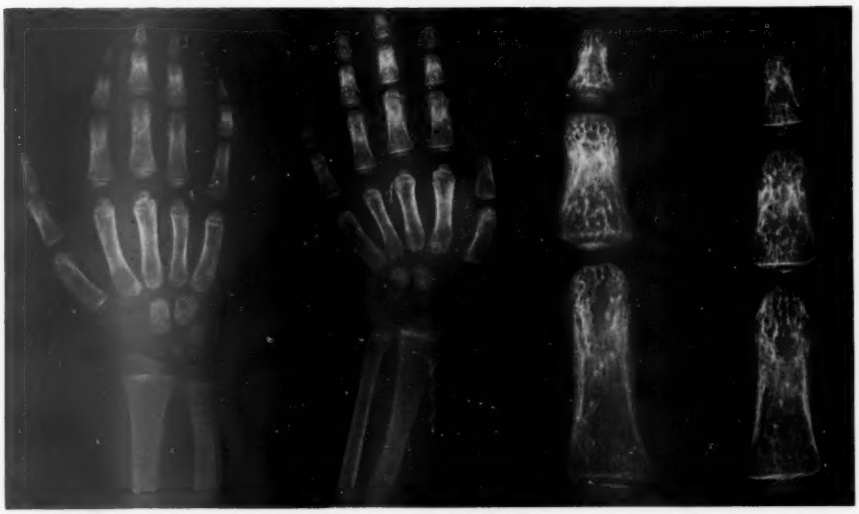

FIG. 6. The radiological appearances of the hand and wrist, and of an enlarged single finger, in the patient and a normal child. The 'control' child was of the same height as the patient, but two years younger. (Simultaneous exposure on the same X-ray plate)

Note the delayed appearance of carpal centres of ossification, the absence of rachitic changes at the radial and ulnar metaphyses, and the thin cortex in all bones of the patient. The thin bone cortex is especially obvious in the distal and middle phalanges of the enlarged finger. It should also be noted that the periosteal surface of the bone is normal and quite smooth; there is none of the subperiosteal erosion that is seen in secondary hyperparathyroidism

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PULMONARY TUBERCULOSIS AND DIABETES MELLITUS[1]

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(From University College Hospital, London)

With Plate 2

In the nineteenth century pathologists observed that active pulmonary tuberculosis was a common finding at post-mortem examination of patients with diabetes mellitus (Griesinger, 1859; Windle, 1883; Williamson, 1898). There have been a large number of reports upon the prevalence of tuberculosis among diabetics and upon the relevant clinical factors predisposing to this disease. Conclusions drawn from these studies will necessarily depend upon the methods used in case finding. Surveys made at diabetic clinics include those in which the diagnosis of tuberculosis has been made only after the onset of respiratory symptoms (Joslin, 1928; Lorenzen, 1929–31; Wendt and Peck, 1931; Kennedy, 1933; Gauld and Lyall, 1947) and those in which routine radiography of the chest has been employed (Root, 1934; Himsworth, 1938). Surveys from sanatoria have studied diabetic patients found among tuberculous populations (Landis, Funk, and Montgomery, 1918–19; Wassmund, 1927; Goldberg, 1946; Banyai and Cadden, 1944; Ferrara, 1952). Recently a mass-radiography survey of a large proportion of the diabetic population of Philadelphia has been performed, and the clinical features of the diabetic subjects with tuberculosis have been compared directly with a control population (Boucot, Cooper, Dillon, Meier, and Richardson, 1952). There have been few reports from Britain; the majority of these are not recent, and they concern only small numbers of cases (Dunlop, 1937; Himsworth, 1938; Gauld and Lyall, 1947).

The present study is based on 104 cases of diabetes with active tuberculosis; about half of the patients came under the care of a hospital for chest diseases, and the other half attended a diabetic clinic where tuberculosis was diagnosed during the course of their supervision. An analysis has been made of the clinical features shown in these two groups. The period of observation has been longer than in many previous reports; 55 patients were followed up for over five years from the time of diagnosis of tuberculosis. An attempt has been made to compare some aspects of diabetes in patients with and without tuberculosis. Sufficient time has not elapsed to assess the full effects of antituberculous drugs on diabetic patients with tuberculosis, but some preliminary observations have been made.

Scope and Methods of the Present Study

1. *Diabetic patients with tuberculosis.* (1) *The Brompton Hospital and the London Chest Hospital.* Between January 1, 1947 and December 31, 1953, 59

[1] Received May 17, 1956.

diabetic patients were admitted with active tuberculosis for treatment. Forty-three were patients with chest disease diagnosed for the first time, and 16 were admitted with a relapse. (2) *University College Hospital.* All patients attending the diabetic clinic of this hospital have had a chest radiograph taken on their first attendance, and subsequent films have been taken at approximately yearly intervals. Between January 1, 1940 and December 31, 1954 the records of the diabetic clinic show 1,851 new attendances, and that 45 of the patients had active pulmonary tuberculosis; in 34 the diagnosis was made at the time of their first attendance, and these cases only have been used for assessing the prevalence of tuberculosis among diabetics. In 11 the disease was discovered during the course of their supervision at the clinic.

2. *Diabetic patients without tuberculosis.* The clinical features of diabetics with tuberculosis have been compared with those of non-tuberculous diabetics, and for this purpose the case records of 843 patients currently attending the diabetic clinic at University College Hospital have been used, correction being made for the variation in sex and age. Conclusions drawn from this comparison must be interpreted with some reserve, as it has not been possible to pair the tuberculous with the non-tuberculous diabetics in all respects.

3. *The prevalence of tuberculosis in the general population.* The prevalence of tuberculosis among diabetic patients has been compared with that found in a sample of the general population, and for this purpose the findings of the Mass Radiography Unit at the Central Middlesex Hospital have been used. In this survey patients have been referred to the unit from two sources: all in-patients have had a routine radiograph taken on their admission to hospital, and also practitioners have referred patients directly to the Unit. During 1953 and 1954, 58,867 radiographs were taken of patients over the age of 15 years. These figures have been used in preference to the statistics from the Ministry of Health (1950–4) because, first, the older age-groups have been analysed in more detail, an essential measure if comparison is to be made with a diabetic population in which large numbers of cases are diagnosed in later life; and secondly, the methods of assessment of activity of tuberculosis more closely resembled those used in the present study. The prevalence of tuberculosis based upon the data from the Central Middlesex Hospital is rather higher than that found by the Ministry of Health (1950–4). It is realized that these figures can be compared only tentatively with the present diabetic series, and that further information on larger numbers of diabetics compared with a more precise control group is required.

4. *Criteria for the diagnosis of tuberculosis.* The diagnosis of tuberculosis was established by the identification of acid-fast bacilli in the sputum in 84 of the 104 patients. Of the remaining 20 cases, three were proved at post-mortem examination or after resection. In eight patients serial radiographs revealed calcification in the healing lesions, which in this country may be considered good evidence of a tuberculous aetiology. Of the remaining nine patients, four had initial cavitation, and serial radiographs showed 'hardening and shrinkage' of the lesions; three others showed similar changes, although initial cavitation

was not present, and two showed gradual clinical and radiological response to antituberculous drugs. These nine patients have been included because the initial clinical and radiological appearances, and the subsequent progress of the disease, left no reasonable doubt as to the diagnosis.

Method of diagnosis. Thirty-three out of 104 patients were diagnosed by routine radiography in the absence of respiratory symptoms, and in 71 the disease was discovered after the onset of general or local symptoms.

TABLE I

The Prevalence of Pulmonary Tuberculosis among Diabetics attending University College Hospital compared with a Control Series from the Mass Radiography Unit, Central Middlesex Hospital

		Control series				Diabetics			
			Pulmonary tuberculosis				Pulmonary tuberculosis		
Age on examination (years)	Sex	Number of persons	Number	Rate per 1,000		Number of persons	Number*	Rate per 1,000	
15–34	M	9,989	48	4·8		128	(0·6) 2	15·6	
	F	19,519	80	4·1		172	(0·7) 6	34·9	
35–44	M	4,999	36	7·25		127	2	15·6	
	F	6,878	27	3·93		133	6	45·2	
	M	4,616 M 12,199	41 M 94	8·88 M 7·7		210 M 557	5 M (4·3) 9	23·8 M 16·2	
45–54	F	4,872 F 14,334	15 F 51	3·07 F 3·5		218 F 629	2 F (2·3) 14	9·2 F 22·4	
55–64	M	2,584	17	6·6		220	2	9·1	
	F	2,584	9	3·48		278	6	21·6	
Over 65	M	1,472	13	8·9		142	(1·3) 2	14·1	
	F	1,354	4	3·0		223	(0·7) 1	4·5	
Total		58,867	290	4·9		1,851	(9·1) 34	18·2	

* Parentheses show the expected number of cases of tuberculosis, assuming that the prevalence of tuberculosis among diabetics and the control population is the same.

Results

Prevalence of tuberculosis among diabetic patients (Table I; Fig. 1). Thirty-four out of 1,851 new diabetic patients were diagnosed as having tuberculosis by routine radiography on their first visit to the diabetic clinic at University College Hospital. If the prevalence of tuberculosis had been the same as in the control population, the expected number of cases would have been 9·1. It is shown in Table I that this increased prevalence can be demonstrated in both sexes and in all age-groups.

Age and sex (Table I; Fig. 1). There was a greater prevalence of tuberculosis among diabetic women than among diabetic men in all age-groups (age at the time of diagnosis of tuberculosis) up to the age of 65, except in the 45–54-years decade; the apparently low figure in this group of patients may have resulted from the small number of cases analysed. In the group of diabetic patients over 65 years of age diabetic men appeared to show an increased prevalence of tuberculosis compared with the control group, but no appreciable difference was demonstrated among the women. Table II shows the sex- and age-distribution at the onset of diabetes in the whole series of patients studied; 66 per cent. were under the age of 40 years. The proportion of young diabetics was greater among patients seen at the chest hospitals than among those seen at the diabetic clinic.

Sequence of disease. Diabetes mellitus was the initial disease in 77 of this series of 104 patients; in 19 tuberculosis and diabetes were diagnosed simultaneously, and in eight tuberculosis was diagnosed first.

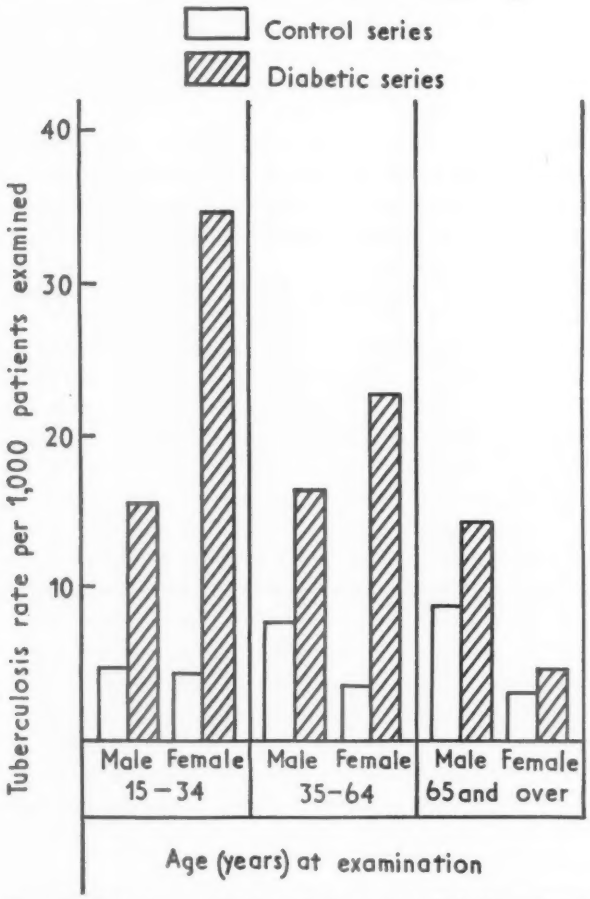

FIG. 1. Prevalence of tuberculosis among diabetic patients (University College Hospital) compared with a control group (Mass Radiography Unit, Central Middlesex Hospital)

Features of Diabetes in Tuberculous Diabetic Patients

The duration of diabetes before the development of tuberculosis was known in 76 patients. No great variation in this respect was found between the individual hospital groups. Of 61 diabetics under 40 years old, 38 (62 per cent.) acquired tuberculosis within the first 10 years of diabetic life; of 15 patients who developed diabetes over the age of 40 and contracted tuberculosis, 93 per cent. acquired the latter disease within the first 10 years. The rapidly declining incidence of tuberculosis after this interval of time is not likely to be due to

the short period of observation, because 38 per cent. of the patients attending the diabetic clinic have been followed up for over 10 years.

The severity of diabetes has been defined arbitrarily in terms of insulin requirements. Although this definition may be misleading in the insulin-resistant

TABLE II

The Age- and Sex-distribution of Tuberculous Diabetic Patients in the Different Hospital Groups

Hospital	All patients			Patients under 40			Patients over 40		
	Total	M	F	Total	M	F	Total	M	F
Brompton Hospital . .	41	24	17	30 (73%)	15	15	11	9	2
London Chest Hospital .	18	8	10	14 (76%)	7	7	4	1	3
University College Hospital	45	17	28	24 (53%)	10	14	21	7	14
Total	104	49	55	68 (66%)	32	36	36	17	19

diabetic, the majority of these patients were from the younger age-group, in which diabetes is more commonly insulin-sensitive.

Degree	*Insulin requirements*
Mild	Nil to 40 units per day.
Moderate . . .	40 to 80 units per day.
Severe	Over 80 units per day.

In the present series 19 diabetic patients under 40 years old (31 per cent.) were having a low insulin dosage, compared with 23 (74 per cent.) diabetics over this age. Twenty-two (36 per cent.) of the young diabetics were receiving large doses of insulin (over 80 units), compared with only two of the 31 older patients.

TABLE III

Severity of Diabetes in Tuberculous and Non-Tuberculous Diabetic Patients

	Age (years)	Mild		Moderate		Severe	
		Number	%	Number	%	Number	%
Diabetics with tuberculosis (92 patients)*	Under 40	19	31	20	33	22	36
	Over 40	23	74	6	19	2	7
Diabetics without tuberculosis (816 patients)	Under 40	70	39	74	42	34	19
	Over 40	492	77	126	20	20	3

* In eight other patients tuberculosis was diagnosed before diabetes, and in four the severity of diabetes was not known.

No significant difference in the severity of diabetes has been demonstrated between patients with and patients without tuberculosis (Table III). This finding differs from that of Boucot, Cooper, Dillon, Meier, and Richardson (1952), who demonstrated that diabetes was more frequently severe in the group of patients who developed tuberculosis; this association was especially striking in diabetics under 40 years old.

Control of diabetes. Assessment of the control of diabetes was based upon the data collected in each case concerning symptoms of thirst and frequency of micturition, glycosuria, and a history of hypoglycaemia and ketosis. There

was insufficient information about change of weight to use this in assessing control. An arbitrary classification of good, fair, and poor control has been used. This assessment must be to some extent a subjective impression, but the same standards have been applied throughout the study. It is shown in Table IV that poor control of diabetes was more common in patients who later

TABLE IV

Control of Diabetes in Tuberculous and non-Tuberculous Patients

	Age (years)	Degree of control: Good Number	Good %	Fair Number	Fair %	Poor Number	Poor %
Diabetics with tuberculosis (control before onset of pulmonary tuberculosis)	Under 40	13	23	9	16	34	61
	Over 40	5	36	2	14	7	50
Diabetics without tuberculosis (control during time of attendance at the clinic)	Under 40	87	50	56	31	35	20
	Over 40	511	72	162	23	42	6

Standard error of the difference:
of 'under 40' groups with poor control: 8 per cent.
of 'over 40' groups with poor control: 14 per cent.

developed tuberculosis. This feature was observed in the younger and older diabetics, but was more noticeable in the younger group.

In previous reports upon this subject good diabetic control has generally been assumed to be important in reducing the incidence of tuberculosis, but little evidence in support of this belief has been put forward. The report by Dunlop (1954) is suggestive, but the number of tuberculous diabetics studied by him was small. In the Philadelphia Survey (Boucot, Cooper, Dillon, Meier, and Richardson, 1952) no such correlation could be found, but this conclusion may have been the result of the limited criteria for diabetic control used in the report.

Control of diabetes and relapse of tuberculosis. If poor control of diabetes predisposes to pulmonary tuberculosis, relapse may be expected to occur more commonly in the poorly controlled patients. Diabetic control has been assessed over the whole period following the onset of tuberculosis; those periods during which patients were receiving in-patient treatment for active disease have been excluded from consideration, as it is probable that active tuberculous infection is a separate factor which will unbalance a normally well-controlled diabetic. Relapse of tuberculosis occurred in 43 patients; the standard of control was known in 39, and was good in 17 (45 per cent.) and poor in 15 (39 per cent.). Thirty had no relapse; the standard of control was known in 29, and was good in 18 (62 per cent.) and poor in only four (14 per cent.). It is unlikely that this difference can be accounted for by chance. The standard error of the difference in the proportion of poorly controlled diabetics, as between the relapsing and non-relapsing groups, is 10 per cent.

Ketosis. The history of ketosis before the onset of tuberculosis was sought

in all patients. A very significantly higher proportion of patients subsequently developing tuberculosis had had episodes of ketosis (Table V).

TABLE V

History of Ketosis in Tuberculous and Non-Tuberculous Diabetic Patients

	History of ketosis			
	Diabetics developing tuberculosis		*Diabetic controls*	
	Number	%	*Number*	%
Total	25/104	24	31/843	4
Patients under 40 years old	22/68	32	23/282	8

Clinical Features of Tuberculosis in a Group of Diabetics

The radiological extent of tuberculosis at the time of diagnosis is shown in Table VI. (In four patients the initial extent of disease was not known.) Among these tuberculous diabetic patients 25 per cent. had lesions in one zone only at the time of diagnosis, and 35 per cent. had lesions in more than two

TABLE VI

The Radiological Extent of Disease compared with the Method of Diagnosis

	Diagnosis					
	Routine X-ray		*Symptomatic*		*Total*	
Extent of disease	*Number of cases*	%	*Number of cases*	%	*Number of cases*	%
1 zone	11	33	14	21	25	25
2 zones . . .	15	46	25	37	40	40
More than 2 zones .	7	22	28	42	35	35
Bilateral . . .	12	37	30	45	42	42
Cavitation . . .	11	33	37	55	48	48

zones; 48 per cent. had cavities. The value of routine radiography is demonstrated in Table VI, where the number of zones affected and the incidence of cavitation are both less in the group diagnosed by this means. It has not been possible to compare the extent of disease in diabetics of different ages, because in this respect they are not distributed evenly between the groups diagnosed by the two methods. The majority of previous reports have agreed that tuberculosis was far advanced at the time of diagnosis, and that this was so whether the investigation was concerned with patients attending a diabetic clinic with respiratory symptoms (Foley and Adosca, 1944; Ralli and Steinberg, 1937–8; Dunlop, 1937), diabetics receiving treatment at sanatoria (Ferrara, 1952), or patients diagnosed by routine radiography (Root (1952) found only 28 patients with minimal lesions among 686 tuberculous diabetics). The Philadelphia Survey, however, (Boucot, Cooper, Dillon, Meier, and Richardson, 1952) found that 63 per cent. of 261 patients had minimal lesions; but only 80 of these patients had active tuberculosis, and the proportion with minimal lesions among this number was not mentioned.

'*Diabetic tuberculosis.*' The specific radiological appearance which has been

reported as common in tuberculous diabetics is characterized by a wedge-shaped opacity, in which there is cavitation, spreading from the hilum and occurring in diabetics over the age of 40 years (Steidl and Sosman, 1927) (Plate 2, Fig. 2). In the present series 11 out of 104 patients showed this radiological appearance, but only six (5·8 per cent.) were over the age of 40. Inspection of lateral films and tomograms showed that a variety of anatomical sites contributed to the single appearance of 'diabetic tuberculosis' on the postero-anterior film (Plate 2, Figs. 2 and 3). In three instances the anterior segment of the upper lobe was predominantly affected, and in one the posterior segment; in two further patients the apical segment of the lower lobe was chiefly affected. It has been suggested that, because the tuberculous process begins deeply in the lung, signs and symptoms in such cases are scanty, and that tuberculosis is therefore far advanced before it is diagnosed (Himsworth, 1938). The 'deep' situation of the lesion is an impression gained from the postero-anterior film; lateral radiographs show that the opacities frequently spread to the chest wall (Plate 2, Fig. 3). A poor prognosis in 'diabetic tuberculosis' has been suggested by some authors (Kennedy, 1933), but has not been found in the present series. Two patients died, two and six years after the diagnosis of tuberculosis; the remaining nine are alive with arrested or quiescent disease. These patients have been followed for periods varying from four to 18 years. In conclusion, no specific radiological features have been discovered in the tuberculous diabetic, and in the few patients whose lesion would conform to that described as 'diabetic tuberculosis' the clinical features and the progress differed from those found in previous reports.

Treatment of tuberculosis (Table VII). Antibacterial drug treatment for tuberculosis became generally available in Great Britain in 1950. Patients included in the present survey have therefore been placed in two categories: (1) those whose treatment was completed before 1950; these patients have been followed for a minimum period of six years; and (2) patients treated after 1950. No major difference in the extent of tuberculosis or in the type of diabetes has been observed between these two groups. Sufficient time has not yet elapsed for the complete assessment of patients treated with antibacterial drugs, but certain features are worthy of comment. Some of the patients with extremely advanced disease have improved remarkably and are surviving after periods up to four years. The use of antibacterial drugs has made it possible to control extensive disease, and allow collapse procedures or resection to be carried out with safety. Before the introduction of drug therapy eight out of 11 artificial pneumothoraces were complicated by hydropneumothorax or empyema, whereas out of 21 patients treated with artificial pneumothorax after 1950 only two developed an empyema. One of the most noticeable features in the treatment of patients after 1950 is that antibacterial drug therapy has caused steady clinical and radiological improvement in patients in whom diabetes was proving almost impossible to stabilize.

Progress. Deaths. Twenty-one of 104 patients have died. Eleven deaths were caused by tuberculosis (10 per cent.), and all the fatalities occurred within

seven years from the onset of the disease; none of these patients received specific drug treatment. No patient of this series receiving antibacterial drug treatment since 1950 has died from tuberculosis. There were four deaths from diabetes, and six were attributed to other causes.

Survivors. Seventy-nine patients were surviving in December 1954; no information was available concerning four. Of 46 surviving patients who have been followed up for over five years from the diagnosis of tuberculosis, the

TABLE VII

Treatment of Tuberculosis in Diabetic Patients

	Category 1		*Category 2*	
Treatment	*Dead* (25%)	*Survivors* (75%)	*Dead* (4%)	*Survivors* (96%)
Rest in bed	2	7	0	3
Antibacterial drugs	0	0	0	57
Pneumothorax	5	6	1	21
(→ Empyema)	(3)	(5)	(0)	(2)
Pneumoperitoneum	1	4	1	13
Thoracoplasty	0	1	0	15
Resection	0	1	0	11
Extrapleural pneumothorax / Plombage	0	0	0	2

Category 1 contains those patients whose treatment was completed before 1950.

working capacity was full in 26 (57 per cent.) and limited in nine (20 per cent.). The remaining 23 per cent. were unable to work, 15 per cent. (seven of the 46) being still under active treatment. The radiological state of the 46 surviving patients followed for a minimum period of five years was assessed: 29 (63 per cent.) had arrested or quiescent disease, and in 36 per cent. tuberculosis was considered to be active.

Discussion

The tuberculosis rate among a group of diabetic patients has been estimated (18·2 per 1,000 diabetics examined). The importance of this figure can be assessed only by comparing it with the rate in a control non-diabetic group. The difficulties in establishing a control figure have been stressed earlier in the present paper, and by Thorn, Brooks, and Waterhouse (1956). The prevalence of tuberculosis among the diabetic patients was lower in the present study than in the majority of previous reports (Table VIII), and the difference may in part be due to the fact that many of the earlier studies included not only those patients who were diagnosed upon their first attendance at the clinic, but also those who were diagnosed while under supervision. The apparent incidence of tuberculosis therefore rose as the period of observation increased. If diabetic patients are predisposed to tuberculosis, the annual attack rate among diabetics known to have had clear chest radiographs would be expected to exceed the normal. It has not been possible to make this calculation from the present data, but a further study is being undertaken. If the annual attack rate among diabetics is greater than in the general population, it will be of importance to know

whether the rate among well-controlled diabetics is also greater. Himsworth (1938) suggested that, once diabetes was well controlled, the risk of developing tuberculosis was no greater than in non-diabetic subjects.

In the majority of previous reports the mortality after the onset of tuberculosis was extremely high. In the largest European series Poulsen (1945–6) found that 91 per cent. of 100 tuberculous diabetics were dead within five years. One of the few encouraging series was that of Himsworth (1938), but in his small group many patients had only minimal lesions, and the period of observation was only two years. All these reports were before the introduction of specific antibacterial drug treatment for tuberculosis. The very high mortality figures in the majority of reports can be correlated with the advanced state of the disease at the time of diagnosis. A relationship between the extent of disease and survival time in uncomplicated cases of pulmonary tuberculosis has been shown by Foster-Carter, Myers, Goddard, Young, and Benjamin (1952). Not only is the mortality among the present group of diabetics lower than in most previous reports, but 14 out of 32 patients treated before 1950 healed their disease and have remained well without relapse for over five years. Good control of diabetes has been shown to be associated with a lower relapse rate, and this factor, together with the smaller initial extent of disease, probably contributed largely to the satisfactory progress of these patients.

TABLE VIII

Incidence of Tuberculosis obtained from Diabetic Clinics using Routine Radiography

		Diabetic patients		
			Pulmonary tuberculosis	
Authors	*Date*	*Total*	*Number*	*%*
Steidl and Sosman	1927	185	16	9
Adams	1929	1,000	10	1
Root	1934	1,659	47	2·8
Himsworth	1938	230	15	6·5
Root and Bloor	1939	364	11*	3
Boucot, Cooper, Dillon, Meier, and Richardson	1952	3,106	(total) 261 (active) 80	8·4 2·6
Present series	1956	1,851	(active) 34	1·8

* Figure calculated from percentage given in the report.

I should like to thank all the physicians and surgeons at University College Hospital, the Brompton Hospital, and the London Chest Hospital for their kind permission to use the case notes and radiographs of patients under their care, and also the many physicians who have answered my requests for information. I am very grateful to Dr. Pygott for allowing me to anticipate his own publication and to quote his findings from the Central Middlesex Hospital.

Summary

1. The prevalence of pulmonary tuberculosis among patients attending the diabetic clinic at University College Hospital between 1940 and 1954 was 18·2 per 1,000 diabetic patients examined. The prevalence among a sample of the general population was 4·9 per 1,000.

2. Age, sex, control of diabetes, ketosis, and the length of diabetic life have been shown to influence the prevalence of tuberculosis.

3. No evidence was found to support the specific radiological appearances described as 'diabetic tuberculosis'.

4. Twenty-five per cent. of diabetics treated for tuberculosis before 1950 died from this disease between three and seven years from its onset. No patient in this study treated with antituberculous drugs has yet died from tuberculosis.

5. The early results of antituberculous drug treatment in tuberculous diabetics have been discussed.

6. Prognosis has been assessed in terms of death, radiological activity, relapse, and working capacity after a period of observation of five years. Factors influencing prognosis were control of diabetes, the initial extent of tuberculosis, and the method of treatment of tuberculosis.

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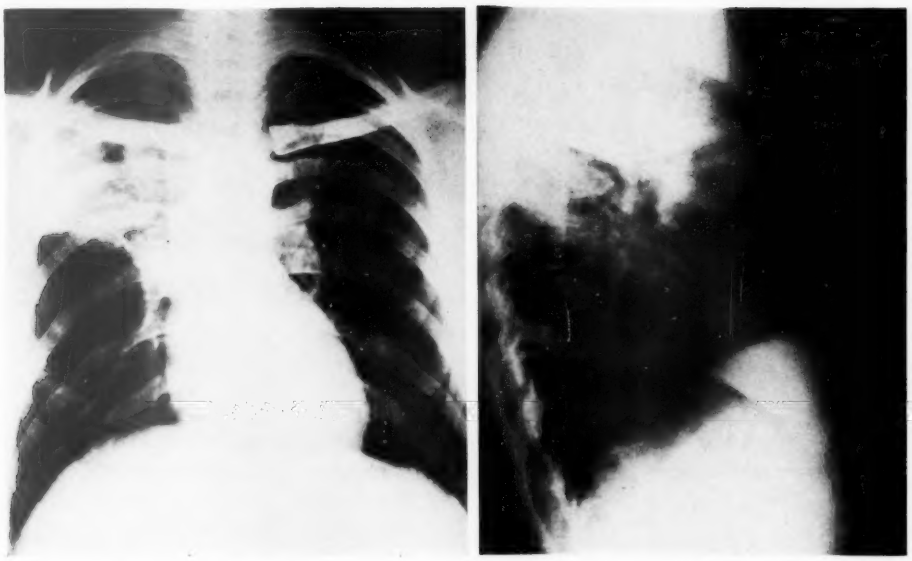
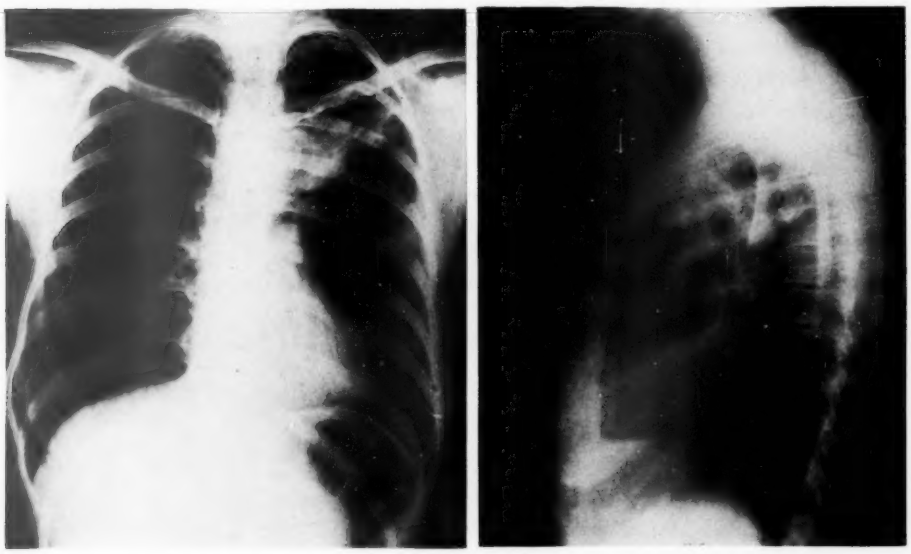


March 1949 (postero-anterior) March 1949 (lateral)

FIG. 2. 'Diabetic tuberculosis.' The wedge-shaped lesion extending from the hilum is associated with cavitation. The lateral radiograph shows the posterior segment of the upper lobe and the apical segment of the lower lobe to be chiefly affected



1948 (postero-anterior) 1948 (lateral)

FIG. 3. 'Diabetic tuberculosis.' In the lateral radiograph the wedge-shaped lesion is shown to affect the anterior segment of the upper lobe chiefly, and to extend to the periphery of the lung

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POLYARTERITIS NODOSA[1]

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With Plates 3 to 7

Polyarteritis nodosa was originally described in 1866 by Kussmaul and Maier; but its manifestations were so varied, and the disease itself seemed so uncommon, that it was rarely diagnosed in life. Introduction of skin and muscle biopsy greatly increased the frequency of diagnosis during life, and led to a much greater interest in the disease. This may partly explain the impression which prevails widely among physicians and pathologists that the disease is now seen much more commonly than a generation ago. Nevertheless, an individual physician or hospital is even now unlikely to have an opportunity of collecting more than a few cases. An inquiry made by one of us into the expectation of life of patients with polyarteritis nodosa provided a unique opportunity for extending our knowledge of the natural history of the disease. The resulting survey, which was initiated by the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council, was made possible by the generosity of nine British teaching hospitals in permitting free access to clinical and histological material from their cases. As a result of their co-operation it was possible to collect a total of 111 cases with histologically proven polyarteritis. Much of the information gained from these cases merely confirmed the experience of earlier writers. The survey did, however, throw new light on a syndrome of polyarteritis nodosa with lung involvement, on the aetiology of the disease, and on the cause of the changes in blood-pressure. These aspects of the disease are discussed in the present paper.

Case Material

The hospitals concerned in the investigation are listed at the end of the paper. An attempt was made to gather the records of all patients with polyarteritis nodosa under the care of these hospitals in the period 1946 to mid-1953. The diagnostic indexes and necropsy records for this period were searched, and the sections taken from all cases diagnosed at necropsy as any form of arteritis were examined. All the 111 cases regarded as proven showed lesions which

[1] Received June 2, 1956

satisfied the following criteria: (*a*) necrosis of the artery with local inflammatory response, *or* (*b*) evidence of previous necrotizing arteritis, as shown by medial scarring and interruption of the internal elastic lamina; *but excluding* (1) cases in which the arteritis was in an area of infection or infarction, to which it might be secondary; (2) cases with evidence of bacterial or mycotic infection spreading from within the lumen and producing the arteritis; (3) giant-cell (temporal) arteritis. The sections from all the possible cases were examined by both of the authors, and doubtful cases were referred to a panel consisting of Professor G. Payling Wright (chairman), Professor C. V. Harrison, and Dr. A. H. T. Robb-Smith, for whose valuable help we are most grateful. In each case accepted into the survey a report on the sections was provided by one of the authors or by a member of the panel. These reports form the basis of the histological data here presented. In addition, three of the pathological illustrations are from cases which were seen by one of us outside the period of the survey.

Seven of the cases were clearly different from the rest, and they have been excluded from the analysis. Briefly, they were as follows: (1) A case of disseminated lupus erythematosus with associated polyarteritis. (2) Three cases in which polyarteritis was a minor necropsy finding, and in which the appearances were atypical. (3) Two cases of polyarteritis confined to the lungs and associated with presumptive evidence of pulmonary hypertension. Similar cases have been described before, and seem to constitute a distinct entity. (4) An infant with multiple aneurysms of large arteries.

PART I. Polyarteritis Nodosa with Lung Involvement

Polyarteritis nodosa may affect almost any organ or group of organs, and consequently its symptoms and signs can be extremely varied. Thus the disease provides a fertile field for the medical taxonomist, and several classifications have been proposed. Of these the two most commonly employed are that of Zeek (1952), and that which distinguishes cases according to the size of artery involved. Neither of these methods was found to apply satisfactorily to cases in the present series, which seemed, however, to fall fairly clearly into two groups, distinguished by the presence or absence of involvement of the lungs. Description here will be limited mainly to the type with lung involvement, since the features of the commoner type, in which the lungs are spared, have already been fully described by (among others) Arkin (1930), Rothstein and Welt (1933), Harris, Lynch, and O'Hare (1939), Grant (1940), Diaz-Rivera and Miller (1946), Miller and Daley (1946), Rose, Littmann, and Houghton (1950), Zeek (1952), and Lovell and Rose (1955).

The possibility of dividing the cases on this basis first came to mind when, at a preliminary analysis of the 104 cases, it was noticed that the lungs were usually completely spared. This was particularly striking when there was severe polyarteritis in almost every other organ. Only 14 patients had definite pulmonary polyarteritis (Group 1 in Table I). On further analysis it was seen that these 14 tended also to show a number of other features which were much

TABLE I

Incidence of Various Features in (a) Patients with Pulmonary Polyarteritis (Group 1), and (b) Patients without definite Pulmonary Polyarteritis who nevertheless showed Several of the Characteristic Features of Group 1 (Group 2)

	Case number	Sex	Age at onset	Cortisone or ACTH	Respiratory illness: Asthma	Respiratory illness: 'Pneumonia'	Respiratory illness: 'Bronchitis'	Upper respiratory granuloma	Glossitis or ulcerative stomatitis	Interval (weeks) between onsets of respiratory illness and systemic polyarteritis	Interval (weeks) between onset of systemic polyarteritis and death	Maximum eosinophilia (cells per c.mm.)	Necropsy findings: Pulmonary polyarteritis	Necropsy findings: Typical necrotizing lesions: Lungs	Necropsy findings: Typical necrotizing lesions: Other viscera	Necropsy findings: Type of polyarteritis: Granulomatous arteritis	Necropsy findings: Type of polyarteritis: Giant cells	Necropsy findings: Type of polyarteritis: Eosinophils numerous	Other data
GROUP 1 (14 patients)	69	M	56	−	−	+	++	−	−	7	2	8,000	+	+	−	−	+	+	No systemic polyarteritis
	70	M	16	−	+	+	++	−	−	?	?	1,700	+	+	+	+	+	+	
	73	F	20	+	+	+	+	−	−	31	134	10,300	+	+	+	+	−	+	Subendocardial Aschoff node
	74	F	32	−	+	+	+	−	−	7 *yrs.*	7 *yrs.*	24,600	+	+	−	+	+	+	
	75	F	48	−	+	+	+	−	−	14	15	8,000	+	+	+	−	−	+	
	76	F	50	−	+	+	+	−	−	10	2	900	+	+	+	+	+	+	
	78	F	49	−	+	+	+	−	−	5 *yrs.*	5	..	+	+	+	−	+	+	Mitral stenosis
	81	M	58	−	−	+	+	−	+	6	18	1,000	+	+	+	−	−	+	Mitral and aortic stenosis
	83	M	64	−	−	+	+	−	+	40	16	100	+	+	+	−	−	+	
	84	F	51	−	−	+	+	+	−	13	4	0	+	+	+	−	−	+	
	85	M	44	−	−	+	+	−	+	0	7	1,150	+	+	+	−	−	±	
	87	M	49	−	−	+	+	+	−	11	1	1,300	+	+	+	−	−	+	Mitral stenosis
	90	M	69	+	−	+	+	−	+	52	124	..	+	+	+	−	+	−	Scleroderma
	93	F	54	+	−	+	+	−	−	130	10	2,000	+	+	+	−	−	−	
	Total	..	7 M	..	3	6	13	7	3	4	..	..	..	14	14	12	9	6	12	
GROUP 2 (18 patients)	67	F	48	−	−	+	−	−	−	0	34	19,900	?	+	+	−	−	−	
	68	F	21	−	+	+	−	−	−	50	28	15,800	..	..	..	(+)	(+)	(+)	No necropsy; details from muscle biopsy
	71	M	32	−	+	−	+	−	−	*c.* 100	*c.* 6	5,800	..	−	−	+	−	+	
	72	M	44	+	+	−	+	−	−	48	8	7,100	..	−	−	+	−	−	
	77	F	54	−	+	−	+	−	−	7 *yrs.*	3	0	−	+	−	+	+	±	
	79	F	42	−	−	−	−	−	+	11	5	150	?	+	+	−	−	−	
	80	F	19	−	+	−	−	−	−	6 *yrs.*	18	11,200	−	−	−	+	−	+	
	82	M	52	−	−	+	−	+	−	8	?2	400	?	+	+	−	+	−	*B. Friedländer* pneumonia
	86	M	51	+	−	+	−	−	−	0	..	100	..	..	..	..	..	..	Alive at time of analysis
	88	F	53	+	−	+	−	−	−	38	23	300	−	+	+	−	−	−	Mitral and aortic stenosis
	89	F	18	−	−	+	−	+	−	5 *yrs.*	31	..	?	+	+	+	+	−	
	91	F	58	+	−	+	−	−	−	11	21	1,500	?	+	−	−	−	−	
	92	M	54	−	−	+	−	−	−	35	8	2,500	?	?	?	?	?	?	Staphylococcal pyaemia, obscuring other pathology
	94	M	31	−	−	−	+	−	+	?	10	0	?	+	+	−	−	−	
	95	M	20	+	−	−	+	−	−	21	27	1,900	..	+	−	−	−	−	
	96	F	35	−	−	+	−	−	−	3 *yrs.*	3	..	?	+	−	−	−	±	
	97	M	41	−	−	+	+	−	−	8	?0·5	..	..	+	−	+	−	−	
	98	M	49	−	−	−	+	−	+	?–7	10	..	−	−	−	+	+	±	Generalized dermatitis
	Total	..	9 M	..	5	6	10	7	2	3	..	..	..	0	11	6	8	5	6	
	Total	..	16 M	..	8	12	23	14	5	7	..	..	..	14	25	18	17	11	18	

less common in the remaining cases (Table II). The most important were a respiratory illness initiating the disease, and the presence in various viscera of unusual necrotizing and granulomatous lesions. In certain other cases with several of the features in Table II it was difficult to be sure whether or not the lungs were involved. For instance, the blocks had sometimes been taken from

TABLE II

Contrasting Characteristics in Cases of Polyarteritis Nodosa With (Group A) and Without (Group B) Lung Involvement

The percentages in this table are based on the numbers of cases in which the relevant data were available, e.g. with regard to eosinophilia, the number of patients with differential white-cell counts.

Manifestation	*Incidence*	
	Group A	*Group B*
1. *Clinical*		
Specific respiratory illness, usually preceding systemic polyarteritis	100%	0
Blood eosinophilia of 1,500 per c.mm. or more	54%	0
Nasal or middle-ear granuloma	16%	0
2. *Pathological*		
(*a*) Lungs:		
Necrotizing lesions (other than typical infarcts and bronchiectasis)	83%	0
Demonstrable pulmonary polyarteritis	54%	0
(*b*) Other organs:		
Numerous eosinophils in polyarteritic lesions	58%	4%
Giant cells present in polyarteritic lesions	35%	0
Granulomatous polyarteritis	55%	6%
Necrotizing or granulomatous lesions not demonstrably related to arteries	60%	0

severely damaged areas, where arteritis might have been secondary to the parenchymal lesions; and in other cases there was no section of lung. Even where there was one adequate section, this did not exclude polyarteritis in other areas. Clearly, then, the presence or absence of pulmonary polyarteritis in the available sections could not be applied as an absolute distinction. A further group was therefore collected, consisting of those cases without adequate lung sections which nevertheless showed three or more of the features listed in Table II; these form the second group in Table I. The 32 cases in Table I have been combined to form Group A of Table II, where they are contrasted with the 66 showing fewer than two of the features in question (Group B). Of the six remaining cases showing two of these features, five had a typical respiratory history, and at necropsy four showed typical necrotizing lung lesions; the existence of pulmonary polyarteritis could not be assessed, in three because no sections of lung were available, and in two because the blocks had been taken from severely damaged lung. In other respects these cases resembled those in Table I, but because the data are so incomplete they will not be considered further. The outstanding contrast was the presence in all cases in Group A, and the absence in Group B, of clinical or necropsy evidence of specific lung lesions (pulmonary polyarteritis, necrotizing or granulomatous lesions, or both).

Group A will therefore be referred to as 'polyarteritis nodosa with lung involvement'. Other differences than those listed in Table II will be mentioned later; but these did not achieve the level of statistical significance.

Case Histories Illustrative of Polyarteritis Nodosa With and Without Lung Involvement

Before contrasting in detail the two groups of cases, three case histories will be given briefly. In the first two patients the lungs were involved; in the third they were spared.

Case 87. A male bus conductor aged 49 years was admitted to the London Hospital on January 11, 1950 with a three weeks' history of earache followed by deafness, discharge, and a right facial nerve palsy. Two months previously he had had an acute febrile illness, diagnosed at the time as influenza.

On examination he showed swinging fever up to 101° F. Both ear drums were perforated and discharging, and the mastoid processes were tender. He had a productive cough, with râles and rhonchi at the right lung base. His blood-pressure was 130/70; the heart was enlarged, and the thrill and murmur of mitral stenosis were present. The blood sedimentation rate was 77 mm. in one hour (Westergren); the white blood count was 25,200 per c.mm., with 21,100 neutrophils and 1,300 eosinophils per c.mm. Bilateral cortical mastoidectomy was performed. The bone was sclerotic, and the air-cells were filled with granulation tissue, which on section consisted of areas of necrosis with surrounding lymphocytes, plasma cells, eosinophils, histiocytes, and giant cells. Chest X-rays showed rounded opacities in both lungs, which were thought to resemble metastases. On January 28 he was found to have proteinuria and a blood-urea of 67 mg. per 100 ml. He died five days later of heart failure.

Necropsy revealed many small grey ulcers in the trachea. The lungs contained scattered discrete nodules up to 4 cm. in diameter, tough and rubbery on section, and traversed by small bronchi and blood-vessels. The heart showed nodules up to 1 cm. in diameter on the coronary vessels, and also mitral stenosis. The spleen was surrounded by dense fibrosis, and on the cut surface were many small nodules. Numerous cortical infarcts were seen in the kidney.

Microscopy showed acute and granulomatous polyarteritis in the lungs, heart, spleen, and kidney; some lesions contained moderate numbers of eosinophils. A number of renal glomeruli were occluded by microthrombi. The lungs showed fibrocaseous pneumonia, but no demonstrable tubercle bacilli.

Comment. The characteristic features of this case with lung involvement are the onset with an influenza-like illness followed by an upper respiratory granuloma, a rapidly downhill course associated with renal failure and eosinophilia, and the finding at necropsy of non-tuberculous caseous lesions in the lungs, tracheal ulceration, pulmonary polyarteritis, and the presence in other organs of granulomatous polyarteritic lesions, some with an eosinophil reaction and others with giant cells.

Case 68. A young woman aged 21 years. In November 1948 she developed a cough productive of thick yellow sputum. The following month she started to have asthmatic attacks, which recurred almost daily. In April 1949 she developed a left-sided pleuritic pain, and on May 18 was admitted to Bangour Hospital. She had by now lost two stone (13 kg.) in weight.

On examination she was thin, and had a persistent tachycardia. Her nose

showed 'allergic rhinitis'. Râles were heard at the right lung base, and X-rays showed faint infiltrations in the mid-zone of the right lung. Sputum, which contained no tubercle bacilli, yielded β-haemolytic streptococci on culture. Blood eosinophils ranged from 1,900 to 15,800 per c.mm. In December she developed diarrhoea with blood and mucus, and thereafter went downhill fairly rapidly, with a haemorrhagic rash, pericardial friction, median neuritis, and hypertension. Muscle biopsy showed granulomatous polyarteritis with giant cells and many eosinophils. She died of severe haemoptysis on May 21, and there was no necropsy.

Case 4. A male Jewish butcher aged 52 years had had typical generalized rheumatoid arthritis for 11 years, treated by numerous courses of vaccine and by three courses of gold. On April 4, 1950 he developed cramp-like pains in the calves. Two days later he noticed swelling of his hands and feet, and a papular rash on his legs. During the next fortnight oedema increased, and the urine became scanty and blood-stained. On April 28 he developed abdominal pain; this and the oedema led to his admission to St. Mary's Hospital. He had so far complained of no respiratory symptoms.

On examination he had irregular fever (up to 100° F.) and tachycardia. His face and limbs were oedematous. The blood-pressure varied from 160/95 to 180/110. Fine râles were heard at the lung bases, and X-rays showed the appearances of pulmonary congestion. The urine contained 1·6 per cent. of protein, and numerous pus-cells and casts. The blood-urea was 50 mg. per 100 ml., and the blood sedimentation rate 68 mm. in one hour (Westergren); numerous white blood counts showed neutrophilia, but no eosinophilia. Muscle biopsy revealed typical acute polyarteritis. At first his general condition improved, fever disappeared, and the blood-urea fell to 36 mg. per 100 ml. Oedema persisted until September 1950, and was associated with continued heavy proteinuria and a decrease of plasma-albumin to 1·8 gm. per 100 ml. Thereafter proteinuria diminished, plasma-albumin increased, and oedema disappeared. In August he developed weakness of the hands and right foot-drop, and was admitted to St. Stephen's Hospital, Chelsea. Subsequently the blood-pressure and blood-urea level rose progressively. He died of left ventricular failure and bronchopneumonia on January 20, 1951.

Necropsy. There was extensive bronchopneumonia, an interlobar empyema, and fibrinous pericarditis. The kidneys weighed 413 gm., and the cortical pattern was obscured. Microscopically the majority of glomeruli were fibrotic; the interstitial tissue was also fibrotic, and infiltrated by chronic inflammatory cells. There was healed polyarteritis of arcuate and interlobular arteries, and also of arteries in the pancreas. No arterial lesions were seen in sections from all the other major viscera, and the lungs showed only congestion and bronchopneumonia.

Comment. The features which help to distinguish this case from those with lung involvement are the absence of clinical and necropsy evidence of any lung lesions other than those due to heart failure and simple infection, the absence of eosinophilia, and the subacute course of the illness, with survival for nine months from the first onset of renal lesions.

The Clinical Features of Polyarteritis Nodosa with Lung Involvement

The sex incidence in this group of 32 patients was equal, as compared with a preponderance of male patients in a ratio of 1·6 to 1 in cases without lung involvement. The age at onset ranged from 16 to 69 years, the incidence rising

steadily throughout life to a maximum in the sixth decade. Contact with tuberculosis was noted in six patients, and had been close in three. No patient gave a family history of asthma or hay fever.

The respiratory illness. All patients had a respiratory illness at some stage, and in 13 of them it was the main cause of death. Respiratory symptoms

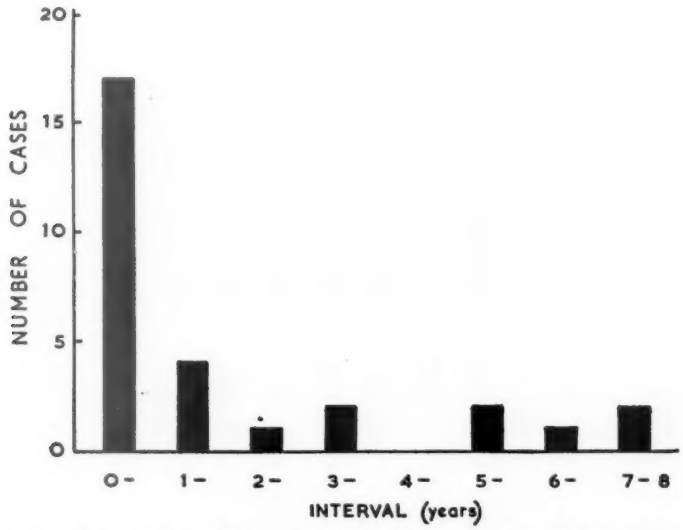

FIG. 1. Distribution of intervals between the onset of respiratory illness and systemic polyarteritis.

initiated the disease in all but one patient. The intervals between the onsets of respiratory and systemic disease are shown in Fig. 1 (excluding one case in which respiratory symptoms followed systemic disease, and two in which the interval could not be assessed). The interval varied up to seven years, and was less than a year in 18 patients. It tended to be longer in those with asthma: thus it exceeded a year in 67 per cent. of those who had asthma, but in only 17 per cent. of those without it. Three main clinical types of respiratory disease could be distinguished, namely bronchitis, asthma, and pneumonia. Patients with *bronchitis* had a productive cough, generally associated with diffuse rhonchi, coarse râles, and prolongation of expiration. Some cases were diagnosed as simple chronic bronchitis, although progressive loss of weight and general weakness suggested more serious disease. *Asthma* occurred in three male and nine female patients. It was usually preceded by a productive cough, which persisted throughout the disease. Attacks tended to be severe and frequent, although occasionally remissions lasted up to 18 months. High blood eosinophilia was usual. In patients with *pneumonia* the commonest symptoms were a productive cough, haemoptysis, and pleuritic pain. Examination generally revealed a localized area of medium or fine râles. The pneumonic episodes were sometimes transient, but more often progressive. They did not respond to

antibiotic therapy; seven patients died from respiratory failure, two from haemoptysis, and two from rupture of an abscess. Pleural effusions developed in five patients. The fluid was lymphocytic or seropurulent, and sterile on culture. Seven patients developed finger clubbing.

Sputum in most patients was abundant and purulent. In six it contained

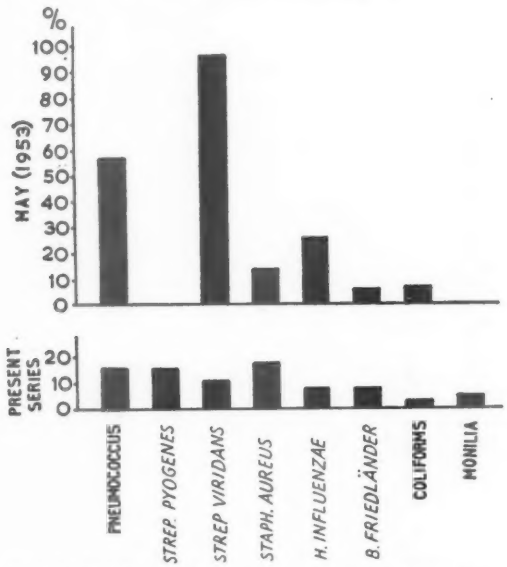

FIG. 2. Incidence of potential pathogens in sputum, comparing the results with those of May (1953).

many eosinophils. Examination for ova, cysts, and mites was undertaken in three cases; none were seen. Table III and Fig. 2 show the results of culture as compared with those of May (1953), who examined 54 sputa from patients with chronic bronchitis. β-haemolytic streptococci were isolated from 23 per cent. of patients, or from 16 per cent. of sputa, in the present series, but from none of May's cases. Direct examination for tubercle bacilli was made on 69 sputa from 22 patients; all were negative.

The chest was X-rayed at least once in 26 patients. Table IV shows the incidence of the various lesions found, some of which are illustrated in Plates 3 and 4. Areas of consolidation appeared at some stage in three-quarters of the patients, but showed no uniform or characteristic pattern. Some produced numerous soft miliary opacities. Of the larger lesions, some were soft, localized, and discrete, while others were dense, widespread, and confluent. Their borders tended to be ill defined, and did not often correspond to lobar boundaries. Upper and lower lobes were involved with equal frequency. In serial films lesions were often seen to disappear at one site and reappear elsewhere; the total duration of those which resolved varied from two to 12 weeks. In one patient healing was associated with calcification. A radiological diagnosis was made of

malignant metastases in three patients, of tuberculosis in at least three, of inhalation abscess in one, and of sarcoidosis in another.

Nose and ears. Persistent nasal obstruction and catarrh developed in nine patients, generally at, or soon after, the onset of the disease. Examination showed ulcerating granulomatous lesions in four of them, and a non-ulcerative

TABLE III

Incidence of Potential Pathogens in 38 Specimens of Sputum from 22 Patients, comparing results with those of May (1953)

Organism	*Number of patients from whom isolated*	*Number of times isolated*	*May (1953)*
Pneumococcus	5 (23%)	6 (16%)	57%
Strep. pyogenes	5 (23%)	6 (16%)	0
Strep. viridans	4 (18%)	4 (11%)	96%
Staph. aureus	6 (27%)	7 (18%)	13%
H. influenzae	3 (14%)	3 (8%)	26%
Friedländer's bacillus	2 (9%)	3 (8%)	6%
Coliform bacillus	1 (5%)	1 (3%)	7%
Monilia	2 (9%)	2 (5%)	0

rhinitis in the remainder. Granuloma of the middle ear occurred in two, one of whom also had a nasal granuloma. It appears from previously reported cases that nasal granuloma in polyarteritis nodosa is confined to cases with lung involvement (see, for example, the cases reported by Lindsay, Aggeler, and

TABLE IV

Chest X-ray Appearances in 26 Patients

Appearance	*Number of patients*
Normal	4
Heart failure changes	7
'Consolidation'	16
Near miliary	3
Larger, round, homogeneous areas	3
Irregular areas	10
Cavitation	4
Pleural effusion	3
Calcification	1
Cystic bronchiectasis	1

Lucia, 1944; Weinberg, 1946; Howells and Friedmann, 1950; Woodburn and Harris, 1951; Stratton, Price, and Skelton, 1953; Godman and Churg, 1954; Walton and Leggat, 1956).

The illness associated with systemic generalization. In general, the illness which followed the spread of polyarteritis to systemic organs resembled that seen in cases without lung involvement. Description will be limited to its distinctive features. By contrast with the frequently insidious onset of respiratory symptoms, the appearance of systemic polyarteritis, which usually coincided with the height of the respiratory illness, tended to be abrupt and to be followed by rapid deterioration in the patient's condition. Hypertension was absent throughout the disease in 77 per cent. of patients, as compared with only 44 per cent.

of those without lung involvement. This difference was associated with a lower incidence of healed renal lesions in cases with lung involvement, a feature which may have been due to their relatively short survival after the onset of systemic polyarteritis. Glossitis, usually ulcerative, occurred in one-quarter of the patients with lung involvement, but in only one of the remainder. Abdominal

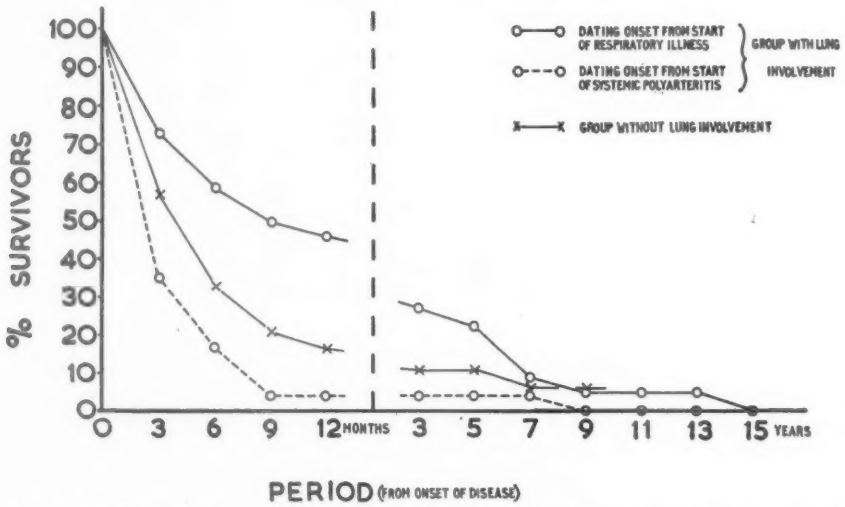

FIG. 3. Course of the disease in patients with and without lung involvement, excluding those treated with cortisone.

manifestations were similar in the two groups, but tended to appear earlier in patients with lung lesions, most characteristically in the form of episodes of bloody diarrhoea; at necropsy such cases often showed extensive superficial ulceration of the alimentary tract.

Eosinophilia. One of the characteristics of the group was the frequency of eosinophilia. Data regarding this feature were mostly obtained during the systemic phase of the illness. A count of 1,500 or more per c.mm. was observed at some stage in 14 patients (54 per cent. of the 26 patients whose differential white-cell counts were available). Another four had maximum counts of 500 to 1,400 per c.mm. The count often fluctuated widely: in one patient it ranged from 50 to 10,300, and varied in a single day from 53 to 1,181 per c.mm. Eosinophilia exceeding 5,000 per c.mm. was seen in 64 per cent. of patients with asthma, but in only 13 per cent. of those without it (excluding patients with no recorded white-cell count).

Outcome and duration of the disease. Eight of the 32 patients were treated with cortisone or corticotrophin. Only one (a cortisone-treated patient) survived when the analysis was completed, and he has since died. All but one patient had active disease at the time of death. The numbers of deaths occurring in various periods of the disease are shown in Table V, and the percentages of survivors in Fig. 3. It was impossible to date the onset of the respiratory illness

in two patients, and the appearance of systemic polyarteritis in one. The figures for patients without lung involvement are given for comparison. Cortisone-treated patients have been excluded. The duration from the onset of the respiratory illness to death ranged from three weeks to 14 years; 12 patients died within a year, and five survived for five years or more. The duration from

TABLE V

Course of the Disease in Patients With and Without Lung Involvement, excluding Patients treated with Cortisone

	Group with lung involvement					
	Dating onset from start of respiratory illness (22 patients)		*Dating onset from appearance of systemic polyarteritis (23 patients)*		*Group without lung involvement (54 patients)*	
Period	*Deaths*	*Survivors (%)*	*Deaths*	*Survivors (%)*	*Deaths*	*Survivors (%)*
0–3 months	6	73	15	35	23	57
3–6 „	3	59	4	17	13	33
6–9 „	2	50	3	4	7	21
9–12 „	1	46	0	4	2	17
1–3 years	4	27	0	4	3	11
3–5 „	1	23	0	4	0	11
5–7 „	3	9	0	4	3	6
7–9 „	1	5	1	0	0	6
9–11 „	0	5	0	0	..	..
11–13 „	0	5	0	0	..	..
13–15 „	1	0	0	0	..	..

the onset of systemic polyarteritis to death ranged from one week to seven years; but 15 patients died within three months, and only one survived more than nine months. The duration was similar in male and female patients. Of patients without lung involvement, 43 per cent. died within three months, and 21 per cent. survived more than nine months. The causes of death in patients with and without lung involvement are shown in Table VI. Death was sometimes attributable to involvement of more than one organ, and was also usually accelerated by the severe constitutional illness. Nearly half of the deaths in patients with lung involvement were due to the specific lung disease. This was chiefly offset by a relatively lower incidence of deaths from healed renal polyarteritis with hypertension.

Only 11 patients were correctly diagnosed in life, and then not until after the appearance of systemic polyarteritis. Six were diagnosed within the first three months of the systemic illness, and also within two weeks of their first admission to hospital. Biopsy proof of the diagnosis was obtained in seven patients; in two others no biopsy was taken. Biopsy of muscle, selected 'blindly', was successful on three out of five occasions, and of skin lesions on each of two occasions. The other two positive results were obtained respectively from the temporal artery and from connective tissue around a lymph-node.

Necropsy Findings

The distinctive pathological features of cases with lung involvement included characteristic necrotizing lesions, seen most commonly in the lungs, but sometimes also in other viscera; and certain peculiarities of the arterial lesions. These features will now be described.

Appearance of the lungs. Evidence of lung destruction was seen in all but one

TABLE VI

Causes of Death in 31 Patients With Lung Involvement and 55 Patients Without Lung Involvement

Cause of death	Incidence: Group with lung involvement — Number of patients	%	Group without lung involvement — Number of patients	%
Polyarteritis in:				
Kidneys	8	26	36	65
Acute polyarteritis with renal failure	3	9	10	18
Healed polyarteritis with hypertension	2	6	15	27
Glomerulitis, initial phase with renal failure	2	6	8	15
Glomerulitis, chronic phase with hypertension	1	3	3	5
Heart	5	16	8	15
Stomach and intestines	2	6	5	9
Central nervous system	0	0	4	7
Specific lung disease:	13	41	0	0
Pneumonia	7	23	0	0
Chronic abscess	2	6	0	0
Haemoptysis	2	6	0	0
Asthma	2	6	0	0
Other causes	5	16	8	15

case, and was visible to the naked eye in all but five. The macroscopic lesions fell into four main groups: (1) necrotic and caseous lesions; (2) atypical consolidations; (3) infarcts; and (4) bronchiectasis. The appearances were not closely related to the length of history, nor to the presence or absence of asthma.

1. *Necrotic and caseous lesions* (15 cases). The appearances in this group closely resembled tuberculosis, and were quite distinct from the infarcts caused by pulmonary emboli. They ranged from minute tubercle-like foci up to massive destruction of most of a lobe (Plate 5, Fig. 7). Nodular lesions were seen in nine cases, with central cavitation in two. The nodules were usually scattered more or less evenly throughout the lungs, and ranged in diameter from 0·1 to 4 cm. The larger ones were sometimes encapsulated. Their cut surface was usually grey or yellow. Sometimes they coalesced to form larger masses. Five patients had fibrocaseous disease, interpreted at the time as tuberculosis; two of these showed cavitation, and in one there were calcific foci. The larynx and trachea were sometimes extensively ulcerated (Plate 5, Fig. 8).

2. *Atypical consolidations* (five cases) were described as areas of 'chronic' or 'haemorrhagic' pneumonia, with cavitation in two cases. We did not have an

opportunity of examining such lesions personally, and it is possible that they were not really distinct from those considered in the preceding paragraph.

3. *Infarcts.* In two cases, neither of which showed any apparent source of embolus, there were many small recent infarcts scattered subpleurally throughout both lungs. Microscopic evidence of infarcts in other cases was also common.

4. *Bronchiectasis* was noted in six cases. In three it was related to nodular or fibrocaseous lesions, and the dilatation affected the smaller bronchi. One case showed gross cylindrical bronchiectasis as the only macroscopic lung lesion.

Sections of lung were available from 24 cases. Definite pulmonary polyarteritis was seen in 14; in four others the sections did not permit adequate assessment. In cases with macroscopic evidence of necrosis, microscopy showed areas of complete lung destruction (Plate 5, Fig. 9), in which, however, the ghost outlines of the tissues were still discernible. These areas were surrounded by giant cells of foreign-body or Langhans type, lymphocytes, and plasma cells, and often also by neutrophils. Histiocytes and eosinophils were usually scanty. No acid-fast bacilli were seen, despite careful search. Some small lesions (Plate 6, Fig. 10) were surrounded by fibroblasts, which tended to form a palisade. Outside the larger lesions there was much fibrosis. Adjacent medium-sized branches of the pulmonary arteries and veins often showed much intimal proliferation of loose connective tissue and a generalized infiltration with neutrophils or eosinophils. The media, especially of arteries, had often undergone fibrinoid change, associated sometimes with small giant cells (Plate 6, Fig. 11). Capillary lesions were sometimes seen, both in the surrounding fibrous tissue and in areas of normal lung. These were characterized by fibrinoid change, nuclear karyorrhexis, outpouring of fibrin, and an accumulation of neutrophils. It seemed possible that these lesions might be the starting-point of the larger areas of necrosis. Diffuse and focal eosinophil infiltration was seen in cases with a high eosinophilia at the time of death.

Microscopy of the upper respiratory granulomata showed a proliferative reaction with infiltration by lymphocytes, plasma cells, neutrophils, and histiocytes, and sometimes also by giant cells (Plate 6, Fig. 12). No polyarteritis was seen.

Necrotizing and granulomatous lesions in other organs. Necrotizing or granulomatous lesions not demonstrably related to arteries were seen in the kidneys (10 cases), liver (eight cases), spleen (six cases), heart (two cases), and lymph-nodes (two cases). They were sometimes very numerous. Macroscopically they formed pale, rounded foci, up to 0·4 cm. in diameter. In the kidney and spleen they were scattered throughout the organ, but in the heart they were subendocardial (though Churg and Strauss (1951) found them mainly in the pericardium). Microscopically they were of several types. In the smallest lesions a focus of necrosis was surrounded by an acute inflammatory reaction in which eosinophils were usually predominant. In others, some of which resembled miliary tubercles, eosinophils were replaced by chronic inflammatory cells, sometimes including giant cells. Occasionally they were associated, as in the lungs, with larger fibrocaseous lesions. In one case a fibrinoid change in collagen,

not associated with arteritis, was seen in the endocardium, aortic intima, and capsule of the spleen.

The appearance of the arterial lesions was similar in the lungs and in the systemic organs. Recent lesions were much more numerous than healed ones in all but one case. By contrast, in the group without lung involvement healed

TABLE VII

Incidence of Polyarteritis in Various Organs at Necropsy

	Incidence of polyarteritis	
	Group with lung involvement (30 cases)	*Group without lung involvement (54 cases)*
Lungs (pulmonary arteries)	47%	0
Heart	60%	35%
Kidneys: Glomerulitis	57%	30%
Renal polyarteritis	60%	65%
Stomach and intestines	40%	30%
Liver	37%	54%
Pancreas	17%	39%
Spleen	43%	35%
Brain	3%	4%
Peri-adrenal connective tissue	40%	41%
Voluntary muscle	33%	20%

lesions were commoner than acute. Most lesions were in small arteries (less than 500μ in external diameter), although in 14 cases larger vessels were also involved. In nine cases no macroscopic evidence of arteritis was seen. Lesions in cases without lung involvement tended on the whole to involve slightly larger arteries. Aneurysms were seen only once in association with lung involvement, but in 10 cases in which the lungs were spared. The distribution of arterial lesions in cases with and without lung involvement is shown in Table VII. The numbers of available sections from the various organs were comparable in the two groups. The chief contrast is of course in the incidence of pulmonary polyarteritis. Coronary lesions were commoner in cases with lung involvement. The bronchial vessels, and all other systemic arteries, seemed to be equally affected in the two groups.

Individual arterial lesions in cases with lung involvement were characterized by a tendency towards the presence of much 'fibrinoid' material, many eosinophils, and a granulomatous reaction. In some cases all lesions were of one or other of these types, but in others a majority were indistinguishable from those seen in cases without lung involvement. In acute lesions the amount of 'fibrinoid' material tended to be greater, and swelling of the internal elastic lamina to be less, in cases with lung involvement. In 16 patients (53 per cent.) there were numerous eosinophils; five others had received cortisone or corticotrophin, drugs which reduce circulating eosinophils. Subacute lesions were often granulomatous (Plate 7, Fig. 13), especially in the spleen and kidney. Lesions resembling tubercles formed in and around the damaged vessels, obscuring their structure. Isolated lesions were occasionally indistinguishable from giant-cell (temporal) arteritis (Plate 7, Fig. 14).

Comparison of Cases With and Without Lung Involvement

The chief contrasts have been shown in Table II. Cases with lung involvement were characterized by a respiratory illness which could be distinguished from disease due to simple infection or heart failure, and which was associated with the presence of specific pathological lesions. This illness nearly always preceded the appearance of systemic polyarteritis, sometimes by years. The total duration of the disease tended to be considerably longer in patients with lung involvement; but their survival after the onset of systemic polyarteritis was shorter. Probably as a result of this, hypertension and healed polyarteritis were less frequent. A prominent feature was a tendency to eosinophilia (over 400 per c.mm.). This was observed in 69 per cent. of patients whose differential white-cell counts were recorded, and in 54 per cent. the count reached 1,500 or more per c.mm. By contrast, a count of over 400 per c.mm. occurred in only 30 per cent. of those in whom the lungs were spared, and in these patients it never exceeded 1,300 per c.mm. Upper respiratory granulomata occurred in five patients with lung involvement; such lesions seem not to occur in polyarteritis nodosa without lung involvement. Cases with lung involvement showed three major anatomical peculiarities. First, the pulmonary arteries were often involved; and in most cases where this could not be demonstrated material was scanty. Second, unusual caseous or granulomatous lesions were found, particularly in the lungs, but in other viscera also in over half the cases. Third, the arterial lesions themselves tended to be distinctive in showing numerous eosinophils in the acute stage and a granulomatous reaction, sometimes with giant cells, during the stage of healing. Granulomatous polyarteritis was rare in cases without lung involvement, and was only once seen outside the spleen; giant cells were never seen. Mucosal ulceration of the alimentary tract and of the trachea was commoner and much more extensive in cases with lung involvement.

By contrast, the two groups were similar in their age-distribution, and in the incidence of polyarteritis in all organs except the lungs and heart. An apparently identical glomerulitis occurred in both syndromes. Most cases with lung involvement showed many arterial lesions which were indistinguishable from those seen in the absence of lung involvement. An association between both types of case and preceding chronic respiratory infections, rheumatic fever, and rheumatoid arthritis, will be described later. On the present evidence it is impossible to state whether the two syndromes represent distinct diseases or merely variants of the same condition. It is to be hoped, however, that these observations may permit a better understanding of the disease, and in particular that they may promote earlier and more frequent recognition of an unfamiliar lung condition. It remains to be seen whether this division of cases is related to differences in aetiology, and also whether it will prove to be any guide to prognosis in patients treated with cortisone for long periods.

Diagnosis

The possibility of polyarteritis nodosa should always be considered in any atypical lung disease associated with asthma, chronic pneumonia, or eosinophilia, especially if there is unexplained disease in other organs. Muscle biopsy may provide proof of the diagnosis. The question is raised, however, whether cases can be diagnosed before the onset of systemic polyarteritis. On clinical grounds it seems impossible to distinguish the respiratory phase of polyarteritis nodosa from the more severe cases of pulmonary eosinophilia as described, for example, by Crofton, Livingstone, Oswald, and Roberts (1952). The lung pathology in such cases is quite unknown; it is of course possible that it is the same as in polyarteritis nodosa. More information is needed as to the outcome of the disease in these patients, and on the question how many of them ultimately develop generalized polyarteritis.

Relation to Other Diseases

Tuberculosis. Six patients in this series gave a history of tuberculosis among first-degree relatives. Half of the necropsy cases showed nodular or caseous lung lesions, and seven showed cavities. Microscopically a few lesions closely resembled miliary tubercles. Only two reports have been found in which tubercle bacilli have been demonstrated in a case of polyarteritis nodosa (Symmers and Gillett, 1951; Tomenius, 1949). In at least eight others it is stated that tuberculous lesions were present, but the actual demonstration of tubercle bacilli is not recorded (Ferrari, 1903; Vance and Graham, 1931; Herrman, 1933; Wechsler and Bender, 1942, Case 3; Jones, 1942, Case 7; Banowitch, Polayes, and Charet, 1942, Case 5; Contratto, 1947, Case 1; Karani, 1953). In the absence of bacteriological proof the evidence from these cases is unacceptable. Rosenthal (1949) described a clinically typical case of sarcoidosis, confirmed by biopsy, which at necropsy showed renal polyarteritis. Guinea-pigs inoculated with an emulsion of the patient's hilar lymph nodes developed granulomatous lesions containing acid-fast bacilli. In the present survey the following evidence makes it unlikely that tuberculosis was a causal factor: (1) No tubercle bacilli could be found in 69 specimens of sputum from 22 patients, including 22 specimens from the seven patients with necropsy evidence of lung cavities. Sections stained for tubercle bacillii from three patients with caseous lung disease were also negative. (2) Radiologically many lesions resolved much more rapidly than would have been expected in tuberculous disease of similar extent. (3) Cases of polyarteritis nodosa with lung involvement often show necrotizing or granulomatous lesions quite distinct from those of tuberculosis. Only a minority cause confusion, and intermediate stages occur between these and the lesions typical of this group of cases.

Bronchial asthma. Most writers have regarded asthma in polyarteritis nodosa as ordinary (allergic) asthma. The present data, however, suggest that it is a specific part of the disease. The evidence for this view will be presented in Part II of the paper.

Parasitic infestations. The frequent presence of high eosinophilia in this syndrome justifies a search for evidence of an association with parasitic infestations. In the present series such evidence was lacking. Negative examinations for ova, cysts, and parasites were recorded in both stools (seven patients) and sputum (three patients). Trichiniasis has been demonstrated in three cases of polyarteritis nodosa (Banowitch, Polayes, and Charet, 1942, Case 5; Reimann, Price, and Herbut, 1943; Movitt, Mackenbrock, and Clement, 1950). This is probably not a significantly high incidence. Ascaris infestation in polyarteritis nodosa with lung involvement has been reported by Perlingiero and György (1947). Of greater interest is the demonstration by Symmers (1954) of larvae, probably those of *Ascaris lumbricoides*, in the lungs in two cases of polyarteritis nodosa. This raises the question of the relationship between polyarteritis nodosa and Löffler's syndrome (Löffler, 1932), since this is now known to be due usually to ascaris infestation (Maier, 1943). Löffler's syndrome, however, is transient and usually symptomless, whereas polyarteritis nodosa in the lungs is disabling and usually progressive. But in view of Symmers's observations it would still be worth searching carefully for evidence of ascaris in future eosinophilic cases. Unfortunately the term 'Löffler's syndrome' has sometimes been applied to cases quite different from those described by Löffler himself. Some of the patients in question have had an illness resembling polyarteritis nodosa, and in at least two cases necropsy has revealed polyarteritis (Bayley, Lindberg, and Baggenstoss, 1945; Buckles and Lawless, 1950).

Pulmonary polyarteritis in association with pulmonary hypertension. Necrotizing pulmonary arteritis has been observed in a number of cases of pulmonary hypertension (Parker and Weiss, 1936; Jones, 1942, Case 13; Old and Russell, 1950; McKeown, 1952; Symmers, 1952; Hicks, 1953; Braunstein, 1955). In each instance the arteritis was confined to the lungs, and probably occurred as an acute terminal episode following long-standing pulmonary hypertension, the latter generally being due to mitral stenosis. In the five cases described by Parker and Weiss necrosis was confined to arterioles, and there was no surrounding inflammation. Lesions in the other cases, however, were inflammatory, and often involved small arteries as well as arterioles. At the beginning of the present paper seven cases were mentioned which, for various reasons, were excluded from the analysis. Among these were two in which lesions were confined to small pulmonary arteries, and in which there was suggestive necropsy evidence of pulmonary hypertension. One had mitral stenosis, and the other emphysema. Plate 7, Fig. 15 shows a typical lesion from the first of them. It seems that, where pulmonary hypertension precedes the onset of pulmonary polyarteritis, the latter change is usually confined to the lungs. But the patients with which this paper is concerned did not appear to have pre-existing pulmonary hypertension, except for four with mitral stenosis; and all but one showed necropsy evidence of systemic polyarteritis (and he had granulomata in the liver and kidneys). It is concluded that the two conditions are quite distinct, and that to use the term 'polyarteritis nodosa' for pulmonary arteritis associated with pulmonary hypertension leads only to confusion. The condition seems in some

ways comparable to the systemic arteriolar necroses of malignant hypertension, which are probably a direct result of the high pressure (Wilson and Pickering, 1938; Wilson and Byrom, 1939; Byrom and Dodson, 1948). The pulmonary lesions differ, however, in being usually inflammatory, and in tending to involve small arteries as well as arterioles. Moreover, the systemic necroses are common in patients with a very high diastolic pressure, but the lung lesions occur in only a very few cases of pulmonary hypertension, and not necessarily, it seems, in those with the highest pressures. At present, therefore, it can only be said that this form of pulmonary arteritis appears to have some specific but obscure relation to the high pulmonary arterial pressure.

Historical Background

In 1908 Dickson described a case of generalized polyarteritis in which the lungs showed bronchiectasis and chronic necrotizing interstitial pneumonia with giant cells; no tubercle bacilli could be found. In his review of previously reported cases of polyarteritis nodosa there are two with probable lung involvement. The first (Ferrari, 1903) had a three years' history of respiratory illness preceding generalized polyarteritis, and necropsy showed widespread arteritis, 'tuberculous' ulceration of the intestines, and 'pulmonary phthisis'; it is not stated that any tubercle bacilli were seen. Necropsy in the other case (Mönckeburg, 1905) revealed focal eosinophilic pneumonia, pulmonary polyarteritis, and granulomatous polyarteritis in other organs. In 1923 Ophüls described a patient with numerous eosinophils, pulmonary and granulomatous polyarteritis, and granulomatous lesions in the pericardium. Rackemann and Greene (1939) outlined the syndrome of asthma, eosinophilia, and peripheral neuritis, and found polyarteritis in seven out of eight such cases. Harkavy (1941) described a similar syndrome, but with 'polyserositis' instead of neuritis; two of his eight patients had proven polyarteritis. Wilson and Alexander (1945) reviewed 300 previously reported cases, and pointed out that eosinophilia was present in at least 44 of the 54 patients who had asthma. They regarded the latter as ordinary (allergic) bronchial asthma progressing to polyarteritis nodosa. Weinberg (1946) took a similar view. Zuelzer and Apt (1949) demonstrated eosinophilic granulomata by liver biopsy in three children with asthma and eosinophilia. Sweeney and Baggenstoss (1949) described the lung lesions in seven cases with pulmonary polyarteritis from the Mayo Clinic, but did not appreciate any contrast between them and cases without pulmonary polyarteritis. Churg and Strauss (1951) gave a very full account of the non-arterial granulomata which they found in 13 out of 14 cases with asthma, eosinophilia, and polyarteritis. They regarded this syndrome as distinct from polyarteritis nodosa, and called it 'allergic granulomatosis and angiitis'. Further full accounts of these lesions have been given by Fienberg (1953*a*) and Godman and Churg (1954).

The relation of these cases to other cases of polyarteritis has been a matter of dispute, and this is reflected in the varied nomenclature. Fienberg (1953*a*) pointed out that they have been variously referred to as periarteritis nodosa, eosinophil granuloma, Wegener's granuloma, lupus erythematosus, rheumatic

and pararheumatic disorders, Löffler's syndrome, and granulomatous glomerulonephritis. To this list Fienberg himself added 'disseminated necrotizing granulomatosis and angiitis' (Fienberg, 1953*b*). Engfeldt and Zetterström (1955–6) have recently suggested 'disseminated eosinophilic collagen disease'. From the present study it appears that the characteristic granulomatous lesions are not restricted to cases with asthma, but they do appear to be restricted to cases with lung involvement. The observations also clarify the natural history of this group of cases. The classification proposed by Zeek and her colleagues (Zeek, 1952; Knowles, Zeek, and Blankenhorn, 1953) divided cases of polyarteritis into six groups: (1) hypersensitivity angiitis; (2) allergic granulomatous angiitis; (3) rheumatic arteritis; (4) periarteritis nodosa; (5) temporal arteritis; and (6) unclassified. Cases in her second group would belong to the group described here as polyarteritis nodosa with lung involvement, but would constitute only a part of that group. Attempts to classify the remaining cases according to Zeek's criteria were unsuccessful; in particular, 'hypersensitivity angiitis' could not be clearly distinguished from 'periarteritis nodosa'.

PART II. The Aetiology of Polyarteritis Nodosa

Our present ignorance of the cause or causes of polyarteritis nodosa is reflected in the number of theories that have been put forward. Different authorities have attributed the disease to a specific virus infection (Arkin, 1930), to sensitivity to a wide range of drugs, and to bacterial sensitization; experimental pathologists working with sensitized rabbits, and others working with hypertensive rats, have each claimed that the lesions which they produced were analogous to the human disease. It is likely that the ultimate answer will be derived from clinical investigations planned in advance to test the truth of particular hypotheses: the role of laboratory work and of retrospective clinical studies is simply to suggest the questions which such investigations should attempt to answer. At the moment we have little idea of what the questions should be. The present observations are submitted rather to prompt future inquiry than to justify immediate conclusions. An attempt has also been made to reassess the evidence already presented by other workers.

Results

It was suggested in the first part of this paper that cases of polyarteritis nodosa could be classified according to the presence or absence of lung involvement. Most of the aetiological considerations which follow apply, however, to both groups; where possible, therefore, the two groups will be considered together. The relevant findings can be divided into conditions preceding the onset of polyarteritis nodosa and observations made during the course of the disease.

Infections preceding the onset of the disease. At least 26 patients (25 per cent.) had chronic respiratory infections (as shown by productive cough or suppurative otitis media), which were still active at the time of onset of polyarteritis nodosa (Table VIII). The most striking finding was the high incidence of bronchiectasis

(10 per cent.). Every care was taken to exclude from these figures cases in which the condition might have been secondary to specific polyarteritic lesions; generally the infections preceded polyarteritis nodosa by many years (sometimes from childhood), and they showed no unusual features either bacteriologically or at necropsy. Nevertheless, since polyarteritis nodosa itself is able

TABLE VIII

Incidence of Respiratory Infections Preceding the Onset of the Disease

		Number of cases	
Condition	*Total*	*Group without lung involvement*	*Group with lung involvement*
	104	66	38
Bronchiectasis	10	8	2
Other cases of chronic productive cough	12	6	6
Chronic suppurative otitis media .	4	4	0

to produce such lesions, these observations must be treated cautiously when considering the aètiology of the disease. In nine patients there was either a remote history of rheumatic fever or clinical evidence of chronic rheumatic heart disease. In three more patients the onset of polyarteritis nodosa was accompanied by typical rheumatic fever, and one other patient, with no relevant

TABLE IX

Recent Acute Upper Respiratory Infections

			Throat swab			*Sulphonamides*	
Condition	*Number of patients*	*Interval (weeks) between onset of infection and onset of polyarteritis*	*None taken*	*Strep. pyogenes grown*	*No pathogens grown*	*Number treated*	*Number definitely not treated*
Acute follicular tonsillitis . .	5	2, 2, 2, 2, 3	4	0	1	3	1
Scarlatina . .	1	about 4	1	0	0	1	0
Sore throat . .	6	1, 1, 2, 2, 2½, 3–4	3	2	1	3	2

clinical history, showed a subendocardial Aschoff node at necropsy. This makes a total of 12·5 per cent. of patients with evidence of past or active rheumatic fever (19 per cent. in the group with lung involvement). It is not possible to obtain a satisfactory control group for comparison, but the figures are suggestively high.

In cases with lung involvement there was often a long interval between the onset of the disease and admission to hospital. As a result, information as to minor acute illnesses preceding the original onset of the disease is likely to be unreliable; the data concerning such conditions have therefore been confined to cases without lung involvement (Table IX). In 12 patients (18 per cent.) there was a history of recent acute upper respiratory infection. In at least three

patients this was due to β-haemolytic streptococci; and in five more patients the same aetiology was suggested by the finding of acute follicular tonsillitis. The interval between the onset of the infection and the onset of polyarteritis nodosa varied from one to four weeks; the commonest interval was two weeks. In five other patients there was a history of a cough commencing from one to four weeks before the onset of polyarteritis nodosa, and two others had had an attack of pleurisy in the same period. All but one of these cases came to necropsy, and none showed evidence of lung involvement.

TABLE X

Number of Patients who had received various Drugs within Three Months of Onset of the Disease

Drug	*Number of patients*
Sulphonamides	7
Penicillin	4
Streptomycin	1
Chloramphenicol	1
Arsenic	1
Bismuth	2
Gold	3
Vaccines	4
Cortisone	1

Drug treatment preceding the onset of the disease. The amount of information available as to recent drug administration varied considerably, and was particularly inadequate in cases undiagnosed in life. The results (for patients without lung involvement) are presented in Table X. Four patients were known definitely not to have received sulphonamides, including three of those with recent streptococcal infections. One patient had been treated with 3 gm. of cortisone for rheumatoid arthritis; a month after withdrawal of cortisone the arthritis relapsed, and evidence of polyarteritis nodosa appeared. (Five of the other 65 patients in this group also had a rheumatoid type of arthritis preceding polyarteritis nodosa; none of these had received cortisone.) A history suggestive of drug reactions was recorded in only two patients: (1) One patient developed proteinuria during a first course of gold, given for rheumatoid arthritis 10 years before the onset of polyarteritis nodosa; he had a doubtful reaction during the second course (eight years later); polyarteritis nodosa appeared acutely the day after the second injection of the third course. He had also had swelling of the face and hands eight weeks previously, shortly after a vaccine injection. (2) Another patient had had urticaria four days after an injection of antitetanus serum, four years before the start of polyarteritis nodosa. He also developed a 'high fever' after the first of a course of penicillin injections given for syphilis, six months before the onset of polyarteritis nodosa; it seems that the remainder of the course was uneventful.

Observations made during the course of the disease. The most interesting observations were those relating to sputum culture, drug administration, and the general course of the disease. Sputum culture in cases without lung involvement did not yield any unusual results. Culture was undertaken in 22 of the

32 patients with definite lung involvement (Table III), and β-haemolytic streptococci were isolated from five of them (23 per cent.). It is notable that the β-haemolytic streptococcus is a very rare organism to find in other types of chronic lung disease. The incidence of other organisms in the sputum of patients in the present series was not unusual. Table XI shows the frequency with which

TABLE XI

Various Treatments given during the Course of the Disease

Drug	*Number of patients*
Sulphonamides	24
Penicillin	50
Antihistamines	6
Vaccines	2
Cortisone or corticotrophin	20

the more important drugs were given to patients during the course of the disease. A special search was made for any relation between the administration of drugs and exacerbations of the disease. There was no evidence of any such sequence; such changes as followed their administration were no more than would be expected to result from the natural variability of disease activity. Evidence of drug sensitivity was seen only once, in a patient who developed an itching rash during a first course of sulphonamide; a second course was given later without complication. Even in this patient there was nothing to suggest that the rash (presumably urticaria) was associated with any change in the activity of polyarteritis. In most patients the duration of active disease was prolonged, as assessed by the blood sedimentation rate and by clinical evidence of new lesions. Among the 47 patients who were still alive three months after the onset, the disease was still active in all but one. After one year there was active disease in all but two of the 19 survivors. (These figures exclude the 20 patients who received cortisone or corticotrophin, and also two patients in whom the onset of the disease could not be dated.) In most patients the disease was liable to recurrent exacerbations and partial remissions independently of any treatment given.

Many writers have ascribed polyarteritis nodosa to histamine-type hypersensitivity (for example, Rich, 1946–7; Miller, 1949). In the present survey there was no evidence that manifestations of this type of hypersensitivity occurred with undue frequency. An 'urticarial' rash was recorded in five patients; but the description was convincing in only two of them, and in the other three it is possible that confusion had arisen with the rash of cutaneous polyarteritis. It is in any case to be expected that sensitization might not be uncommon in patients treated with such a wide range of drugs. Eosinophilia, although it was common (especially in patients with lung involvement), cannot be used as definite evidence of hypersensitivity, since it occurs also in a number of diseases in which hypersensitivity is apparently not involved. Asthma was observed in 12 of the 32 patients with definite lung involvement, but the following evidence suggested that it was not ordinary allergic asthma: (1) It occurred

only once in a patient without lung involvement; its duration and severity bore no relation in this case to the course of polyarteritis nodosa, and the patient gave a family history of allergy. (2) None of the 12 patients with lung involvement and asthma gave a family history of allergy. (3) Their ages at onset were typical of polyarteritis nodosa rather than of allergic asthma, that is, the asthma more often began later in life. (4) The asthma was usually associated with a very high eosinophilia (more than 5,000 per c.mm. in half the cases), of an order rarely seen in allergic asthma. (5) Necropsy showed the presence of specific lung lesions, and comparison with clinical and radiological data suggested that these lesions had been present throughout the disease. If it is accepted that asthma in polyarteritis nodosa is not allergic, then it is doubtful whether it provides any useful evidence of hypersensitivity. The characteristic change in polyarteritis nodosa is arterial necrosis and occlusion, whereas the characteristics of urticaria are vasodilatation and oedema; thus the description of polyarteritis as 'urticaria of the blood vessels' (Miller, 1949) does not seem very suitable. States of chronic hypersensitivity, and severe chronic infections, are often associated with a characteristic increase in the γ-fraction of the plasma-globulin. A similar change has been observed in rheumatoid arthritis, disseminated lupus erythematosus, and polyarteritis nodosa. In the present series the plasma-globulin was increased (more than 2·9 gm. per 100 ml.) in 29 of the 44 patients in whom it had been measured; unfortunately electrophoretic studies were not available to identify the particular fraction involved, but experience in cases outside the survey suggests that the increase was mainly in the γ-fraction. Our knowledge of plasma-protein metabolism is too limited to justify any conclusions from this observation; but it is consistent with the hypothesis that these diseases might be associated with a state of hypersensitivity.

Discussion

Polyarteritis in animals

The experimental production of polyarteritic lesions in animals has stimulated the main theories of the aetiology of human polyarteritis nodosa. But each procedure has been shown to produce arteritis in only one or two species of laboratory animal, and in applying the results to human disease due regard has not always been paid to the possibility of species differences. Furthermore, polyarteritic lesions in animals have been shown to result from at least two quite unrelated mechanisms, but both types of lesion have been called polyarteritis (or periarteritis) nodosa. It would be preferable to refer to them simply as examples of 'polyarteritis', and to reserve the more specific name for the human disease.

1. *Hypersensitivity arteritis.* In 1917 Boughton noted that, if guinea-pigs were given repeated injections of egg-white or bovine serum, they developed inflammatory lesions of small visceral arteries; arterial necrosis was not observed. Between 1933 and 1937 a number of German workers produced arteritis in rabbits sensitized to various proteins (horse and swine serum, and casein).

In 1943 Rich and Gregory developed techniques for producing necrotizing arteritis in rabbits treated with horse serum; the same, or similar, techniques have been used by most subsequent workers (for example, Hopps and Wissler, 1946; Hawn and Janeway, 1947; Roberts, Crockett, and Laipply, 1949; More and McLean, 1949; More and Kobernick, 1951; Germuth, 1953). The chief characteristics of this type of arteritis are: (1) Lesions appear in a single crop; in surviving animals they then heal. (2) They affect small visceral arteries and arterioles, especially the branches of the coronary arteries. They are never very numerous, and are entirely absent in some animals; some workers (for example, Alston, Cheng, and Short, 1947) have been unable to produce them at all. (3) Lesions occur less frequently in animals treated with cortisone or corticotrophin (Rich, Berthrong, and Bennett, 1950; Berthrong, Rich, and Griffith, 1950). (4) Glomerulitis is a common associated finding.

2. *Arteritis in rats repeatedly infected with haemolytic streptococci.* Glaser, Dammin, and Wood (1951) described the effects of repeated streptococcal infection in the rat. A suspension of streptococci, derived from a case of rheumatic fever, was injected at intervals of two to three weeks into alternate lungs; each infection was controlled with penicillin. After two to seven injections the animals were killed; segmental necrotizing arteritis was seen in the coronary vessels in 29 per cent. of animals. Similar lesions occurred also in control animals, and in animals infected with pneumococci; but the incidence was significantly greater in the streptococcal group. Apparently only the hearts were examined. If these lesions are analogous to those produced in rabbits sensitized to serum, it suggests that bacterial hypersensitivity also may cause lesions of polyarteritic type.

3. *Hypertensive arteritis.* In 1939 Wilson and Byrom observed necrotizing arterial lesions in rats with arterial hypertension produced by partial occlusion of one renal artery. Some of the lesions were associated with an adventitial inflammatory reaction, and 'in the mesenteric arteries gross changes resembling those of periarteritis nodosa were not uncommon'. Grant (1940), after examining the sections, agreed that the lesions were indistinguishable from those of polyarteritis nodosa in man. Similar observations have since been made by many workers. Various techniques have been used for producing the hypertension, including unilateral nephrectomy, the remaining kidney being wrapped in silk or cellophane (Smith, Zeek, and McGuire, 1944; Zeek, Smith, and Weeter, 1948; Kipkie, 1950; Masson, Hazard, Corcoran, and Page, 1950), a variety of other renal operations (Cromartie, 1943; Loomis, 1946; Hall and Hall, 1951), unilateral nephrectomy and administration of deoxycorticosterone acetate (Selye and Pentz, 1943; Masson, Hazard, Corcoran, and Page, 1950), and feeding with irradiated ergosterol, thus causing precipitation of calcium in the kidneys (Ham, 1940). The arterial lesions have been the same in each instance. Cromartie (1943) and Smith, Zeek, and McGuire (1944) observed that in their experiments the extent of the arteritis was proportional not only to the level of the arterial pressure but also to the severity of the renal infection introduced at operation. Kipkie (1950) suggested that the infection, not the

hypertension, might be the cause of the arteritis. But this would not explain Ham's results in animals given irradiated ergosterol but not submitted to surgery; and Smith and Zeek (1947) were unable to produce arteritis either by submitting the spleen to the same wrapping procedure as that previously used on the kidney, or by wrapping one kidney only (a procedure which did not affect the arterial pressure). It thus appears that necrotizing and inflammatory arterial lesions are a common feature of hypertensive disease in the rat. The characteristics of the lesions are that they involve the main arteries to the viscera, and especially the superior mesenteric artery; they occur especially at bifurcations, but rarely extend into the viscera; they never involve the pulmonary arterial tree; and they produce nodes and aneurysms resembling those seen in polyarteritis nodosa. Smith, Zeek, and McGuire (1944) observed similar lesions in four out of eight dogs with hypertension produced by wrapping the kidneys; but this has not been the experience of other workers on hypertension in the dog (for example, Goldblatt, 1938), or in the rabbit (Wilson and Pickering, 1938). These workers have observed only necrosis of arteries without inflammation. Thus at present there is little evidence that polyarteritic lesions are a feature of hypertensive disease in species other than the rat.

4. *Naturally occurring polyarteritis* has been observed in dogs, rats, swine, cattle, and deer. The subject is fully reviewed by Smith, Zeek, and McGuire (1944). In the case of deer the disease apparently occurred in an epidemic form in a zoo. Wilens and Sproul (1938) studied the cardiovascular lesions in 487 laboratory rats which died of natural causes. Polyarteritic lesions, similar to those seen in hypertensive rats, were seen in 47 of them. It is unfortunate that arterial pressure was not recorded in these animals.

Relation of human polyarteritis to drug administration

There are two possible kinds of evidence for a causal relation between drug administration and polyarteritis nodosa:

1. *Evidence that the administration of a drug shortly preceded the onset of the disease.* This type of evidence depends on the demonstration of such a sequence in a larger number of cases than would be expected to occur by chance; in the case of a commonly used drug the association must be demonstrated frequently. A danger in the use of such evidence is that in some cases the drug may have been given because of, and not before, the onset of the disease. This objection probably applies, for instance, to the case described by Edge, Fazlullah, and Ward (1955). A further difficulty is that, even if a significantly frequent association is established, the relevant factor may not be the drug itself but the condition for which it was given; this applies particularly to drugs used in the treatment of infections. Little useful information can be gained from a retrospective study, such as the present, regarding the relation of drugs to the onset of the disease. In some cases at least the disease appeared in the complete absence of any recent administration of a drug. On the other hand, the data presented in Table X show that a history of recent drug administration, especially of sulphonamides, probably occurred more frequently than would be expected by

chance; case reports in the literature show similar findings. There is little, however, to distinguish between the drug and the condition for which it was given as the relevant factor. In three cases in the present series haemolytic streptococcal infection untreated by drugs shortly preceded the onset of the disease. One recorded case, however, has been found in which polyarteritis nodosa appeared shortly after the prophylactic administration of a sulphonamide to a non-infected patient (Lichtenstein and Fox, 1946).

2. *Evidence that repeated courses of the drug were each related to exacerbations or relapses of the disease.* This type of evidence is potentially much stronger. Its dangers are, first, that sometimes the drug may have been given because of a commencing exacerbation of the disease, in which case it cannot be held responsible for the patient's continued deterioration; and, secondly, that spontaneous variations in the activity of the disease are very common, and may sometimes be fortuitously associated with the administration of a drug. In the present series such evidence was wanting. Allowing for the spontaneous variability of the disease, there was no clear instance of the administration of a drug having an adverse effect on its course. In 24 patients the administration of sulphonamides had no apparent effect on the activity of polyarteritis; it thus seems unlikely that sulphonamides were an aetiological factor in these patients.

There do not appear to be any recorded cases in which repeated courses of sulphonamides bore any clear relation to the activity of the disease. In the case reported by Goodman (1948) polyarteritis nodosa began during the sulphonamide treatment of a sore throat; nine weeks later the inadvertent administration of sulphonamides was followed within 30 minutes by a generalized reaction with urticaria, but one week after this the disease remitted fully and permanently. Although this case is suggestive of sulphonamide sensitivity, it is not clear that this sensitivity bore any relation to polyarteritis nodosa. The increase in the number of recognized cases of the disease during the past 25 years has been advanced as an argument which incriminates the sulphonamides. Since the introduction of the modern antibiotics, however, the use of sulphonamides has become less frequent; yet there is no evidence that the number of cases is falling off. In the present survey, in fact, the evidence is suggestive (although by no means conclusive) that there is a continuing true increase in the incidence of the disease.

Other suspected drugs which did not feature in the present series include serum and thiouracil. In 1937 Clark and Kaplan demonstrated arteritis at necropsy in two cases diagnosed clinically as serum sickness; necrotizing (polyarteritic) lesions were restricted to the testis in one case and to the small coronary arteries in the other. In 1942 Rich described five necropsies, in cases diagnosed as serum sickness, in which there was generalized polyarteritis, and another similar case in which a muscle biopsy showed polyarteritis. The interpretation of these cases should be cautious, since on the one hand the manifestations attributed to serum sickness could all have been due to polyarteritis nodosa; and on the other hand there is now good evidence that respiratory infections (for which serum was given in these cases) are common precursors of

the disease even in the absence of serum therapy. The cases described as developing in association with therapy with thiouracil or similar compounds are of particular interest, because there is nothing to suggest that thyrotoxicosis itself predisposes to the development of polyarteritis nodosa. Three fatal cases have been reported (Gibson and Quinlan, 1945; McCormick, 1950; Dalgleish, 1952) of polyarteritis nodosa which developed during the administration of one of these drugs for thyrotoxicosis. McCormick's patient had exacerbations closely related to four separate courses of the drug, in one instance occurring 12 hours after a test dose of 50 mg.; at necropsy the arterial lesions were not completely typical of polyarteritis nodosa, arterial necrosis being infrequent. In Dalgleish's patient a fatal exacerbation followed a second course of the drug; during the first course the patient had developed an unexplained rash, oedema, and fever, which improved when the drug was stopped. Hicks and Cowling (1952) reported another case, but here the diagnosis of thyrotoxicosis is not absolutely certain; just possibly the patient already had polyarteritis nodosa when the thiouracil was started. Barnum, de Takats, and Dolkart (1951) reported a case clinically suggestive of polyarteritis nodosa, but lacking pathological proof, in a patient treated with thiouracil; Foss (1950) reported a similar case in a patient treated with 2-mercaptoimidazole; and Moore (1946) reported a case with periarterial inflammation but no necrosis. Two cases of thiouracil treatment were considered for admission to the present series, but were rejected. The first was clinically definite, but a biopsy showed only thrombosis and recanalization of a subcutaneous artery; the patient was treated with corticotrophin, and the arteritis remitted. The other patient died, and necropsy showed fairly extensive lesions of small arteries. Most showed only periarterial inflammation, whereas small arteries in the thyroid showed necrosis but no inflammatory response; no arteries showed necrosis and inflammation. The occurrence of rather atypical arteritis in several of the above patients raises the question whether a form of polyarteritis occurs in thiouracil-treated patients which is different from ordinary polyarteritis nodosa. There is at present too little evidence on which to base any answer to this question. The association of thyrotoxicosis with polyarteritis nodosa has been reported only once in the absence of thiouracil therapy (Rich, 1945). In this instance the disease appeared two days after iodine treatment was started. Iodine had also been given to the thiouracil-treated patients reported by Gibson and Quinlan (1945), Foss (1950), and Dalgleish (1952), but, except in the first of these cases, it had been stopped before the appearance of polyarteritis nodosa.

Miller and Daley (1946, Case 6) reported a patient who developed joint pains during treatment with neoarsphenamine bromide. Three months later a further injection of the drug was followed in 24 hours by the acute onset of polyarteritis nodosa, proved at necropsy. Miller and Nelson (1945) reported a case in which polyarteritis nodosa developed during treatment with neoarsphenamine bromide, mapharside, bismuth, and iodides. Other drugs suspected of precipitating the disease include dichlorodiphenyltrichloroethane (D.D.T.) (Hill and Damiani, 1946), dilantin sodium (Van Wyk and Hoffmann, 1948), penicillin (Waugh,

1952), and a combination of penicillin, streptomycin, isoniazid, and cortisone (Edge, Fazlullah, and Ward, 1955). In none of these cases is the evidence very convincing.

Relation to respiratory infections

From the evidence presented earlier it appears that there is a suggestively high incidence of preceding chronic respiratory infections in cases of polyarteritis nodosa. But it is to be pointed out, first, that no satisfactory control group was available, and secondly that the observation must be treated with caution in view of the ability of polyarteritis nodosa itself to produce chronic respiratory disease. Evidence was also presented that in 12 patients (18 per cent. of those without lung involvement) an acute throat infection had occurred within four weeks of the onset of the disease; in at least eight of them the infection was probably due to β-haemolytic streptococci, and in three of these cases it was known definitely that no drug had been given. A similar association has often been recorded by other authors. In a series of 17 cases reported by Spiegel (1936) there was a recent history of tonsillitis in three, scarlatina in one, probable scarlatina in one, and an acute upper respiratory infection of unknown bacteriology in one; in another case recent rheumatic heart disease was found at necropsy. In the youngest recorded patient with polyarteritis nodosa, a child aged eight days, a throat swab grew haemolytic streptococci (Wilmer, 1945).

Relation to rheumatic fever

A possible relation between rheumatic fever and polyarteritis nodosa has been stressed by Ophüls (1923) and by Friedberg and Gross (1934). In the present series there was evidence of past or active rheumatic fever in 12·5 per cent. of patients. Although a similar history has often been mentioned by other observers, the large number of cases with no recorded past history makes it impossible to assess its true incidence. Aschoff bodies have been reported on at least seven occasions in sections of heart from patients with polyarteritis nodosa (Rothstein and Welt, 1933, Case 2; Spiegel, 1936, Cases 1, 8, 10, and 15; Rose, Littmann, and Houghton, 1950, Case 6; Pagel, 1951, Case 1). Necropsy sections from patients with rheumatic heart disease have sometimes shown arteritis. VonGlahn and Pappenheimer (1926) found arteritis in 10 out of 47 consecutive necropsies on such cases. They considered that the lesions could be distinguished from those of polyarteritis nodosa by the absence of thrombosis, by the involvement of small arteries, and by the presence of only scanty eosinophils and plasma cells. But none of these criteria constitutes a valid distinction from polyarteritis nodosa; the only real distinction seems to be the sparseness of the lesions which were observed, as compared with the extensive lesions seen in most cases of polyarteritis nodosa. Whether or not intermediate stages occur is uncertain; but at least such findings are further evidence which suggests a relation between the two diseases. If there is indeed any significant association between rheumatic fever and polyarteritis nodosa, the question arises whether it is simply that the two conditions share a common relation to streptococcal infection, or that some patients may in addition be peculiarly prone to both

diseases. The answer to this question would rest largely on the respective incidence of quiescent and active rheumatic disease in cases of polyarteritis nodosa. Data from the present series were inadequate to assess this point.

Conclusions

It is clear from the preceding results and discussion that there is very little positive evidence from which to infer the causes of the disease, and any conclusions must be tentative. There is no evidence that it is due to a specific infection, dietary deficiency, or endocrine abnormality. It seems very probable that a few cases have been due to hypersensitivity to thiouracil or other antithyroid drugs. This is perhaps the most clear-cut evidence of all; but it applies to very few cases, and there is some slight evidence that thiouracil polyarteritis may be different from ordinary polyarteritis nodosa. The only positive evidence which might lead to an explanation of a large group of cases is the connexion with respiratory infections, especially those due to haemolytic streptococci, and their treatment, especially with sulphonamides. The difficulty is to dissociate these two factors. The following evidence favours incrimination of the infection rather than the treatment:

1. Some patients with recent haemolytic streptococcal infection have received no drug treatment up to the time of onset of polyarteritis nodosa.

2. There appears to be an association between polyarteritis nodosa and rheumatic fever; there is good evidence that the latter disease is related to streptococcal infections, and not to their treatment.

3. If the relevant factor were the sulphonamides, more cases of polyarteritis nodosa might be expected to follow the administration of sulphonamides for other conditions; in fact, in nearly all the reported cases the drug was given for a respiratory infection.

4. The absence of any significant reaction to sulphonamide administration during the course of the disease in 24 patients in the present series suggests that sulphonamide hypersensitivity was not common in these patients.

5. If the disease were due to hypersensitivity to a drug given only at the onset, one would anticipate an initial period of maximum activity, followed by a gradual decrudescence as the sensitizing agent was eliminated from the body. By analogy with known examples of drug reactions (such as serum sickness, or hypersensitivity arteritis in animals), the period of active disease should be relatively short. The observed fact is that, in the present series, all but one of the patients who were alive three months after the start of the disease still had active polyarteritis; and the characteristic pattern of the disease in these patients was one of continuing exacerbations and partial remissions, apparently unrelated to any drug administration. This suggests that, if the disease in these patients was due to an abnormal immune response, the antigen involved was one with which there was prolonged or repeated contact. It is thus unsatisfactory to attribute the disease in this group to a drug given only at the onset. The only drugs which were given repeatedly to most patients were analgesics and barbiturates; there was no other evidence to incriminate either of these.

The disease was active at the time of death in all the 37 patients who died within three months of the start of the disease; it is impossible to predict how long activity of the disease might have continued had they survived (though possibly further experience with cortisone treatment may provide some information on this point). It is reasonable to suppose that it is among these patients, if any, that drug hypersensitivity might be an aetiological factor. Even in this group, however, there was the same suggestively high incidence of respiratory infection.

The available evidence does not warrant any firm conclusions, except that drug hypersensitivity is not a factor in all cases. On the whole it favours an abnormal immune response to bacterial infection as the most likely cause in many cases. The position could be clarified if, in a consecutive series of new cases, an accurate history were taken of any recent drug administration, and a search made as early as possible in the disease for cultural or serological evidence of recent β-haemolytic streptococcal infection. Although it may be that other and quite different mechanisms are involved, it would at least be possible to assess more accurately the two factors which are at present the most strongly suspect. In the meantime it would seem reasonable to give prompt treatment with penicillin to any patient with active or quiescent polyarteritis nodosa who develops an acute throat infection.

PART III. Hypertension in Polyarteritis Nodosa

Hypertension has been widely recognized as a common accompaniment of polyarteritis nodosa, and various attempts have been made to correlate the hypertension with the anatomical findings. Kernohan and Woltman (1938) suggested that it was due to increased peripheral resistance from the widespread occlusion of small arteries. It has, however, been found by others that hypertension is often absent even when polyarteritis is very widespread, and is sometimes present when very few lesions are found at necropsy. Fishberg (1954) suggested that hypertension in polyarteritis nodosa is secondary to extensive involvement of renal arteries. Davson, Ball, and Platt (1948), in a study of 14 necropsy cases, stated that 'the renal findings were . . . varied, and bore no close relation to the presence or absence of hypertension'. They did, however, note that in two of their patients who had severe hypertension necropsy showed healed polyarteritis of the larger branches of the renal artery, and they suggested that in these cases hypertension might have been secondary to renal ischaemia. On the other hand, Zeek and her colleagues (for example, Knowles, Zeek, and Blankenhorn, 1953) concluded that antecedent hypertension had caused polyarteritis nodosa in 21 out of their 45 cases; there is no mention of hypertension developing during the course of the disease in any of their patients. They have suggested a classification of the disease on the basis of this hypothesis, and this has been widely quoted. Ralston and Kvale (1949) also considered that hypertension commonly preceded the apparent onset of the disease. In the following section an attempt is made to correlate blood-pressure

changes with the clinical and necropsy findings in the 104 proven cases in the Medical Research Council series.

Results

The blood-pressure was recorded at least once in 97 patients. But in nine cases the only record was either from an early phase of the disease or terminal; one patient had eclampsia; and another had coarctation of the aorta. The analysis is therefore limited to the remaining 86 patients (53 men and 33 women). The patients have been classified in three groups: (1) Those whose blood-pressure was normal throughout the disease (48 patients); (2) those whose blood-pressure was normal at the initial examination, but who developed hypertension later (17 patients); and (3) those who had hypertension at the initial examination (21 patients). Hypertension is defined arbitrarily as being present if the systolic pressure was 30 mm. or more, or the diastolic pressure 20 mm. or more, above the expected value for patients of the same age and sex, as given by Hamilton, Pickering, Roberts, and Sowry (1954). These expected values are set out in the Appendix. Hypertension is defined as developing during the course of the disease if the systolic pressure rose by 30 mm. or more, or the diastolic pressure by 20 mm. or more, above the first recorded pressure. Any readings which might have been affected by heart failure or peripheral circulatory failure have been excluded. If papilloedema developed in association with a diastolic pressure of 130 mm. or more, the patient has been referred to as a case of malignant hypertension. Papilloedema was not observed in the absence of severe hypertension, although two patients without hypertension developed exudates, and another had haemorrhages around the optic disk. This classification ignores a very small group in which a trivial increase during the course of the disease was sufficient to raise the blood-pressure to just above the upper limit of normal, as defined for the group showing hypertension at the initial examination.

The incidence of the various renal lesions at necropsy in the three groups is shown in Table XII. The 'initial phase of glomerulitis' referred to here is the type described by Davson, Ball, and Platt (1948). The present investigation fully supported the opinion of these workers, who concluded that this type of glomerulitis is a specific lesion of polyarteritis nodosa. In addition, seven patients in the present series survived the initial phase and entered a phase of progressive renal failure and hypertension. At necropsy the appearances in some of these cases were indistinguishable from ordinary chronic glomerulonephritis; the others presented an intermediate picture.

1. *Group with normal blood-pressure* (28 men and 20 women: 56 per cent.). At necropsy this group had the highest incidence of recent glomerular lesions (46 per cent.) and acute polyarteritis of renal arteries (54 per cent.), but the lowest incidence of chronic lesions (16 per cent.). Furthermore, in only two of the six patients with healed renal polyarteritis was there evidence of associated infarction or ischaemic fibrosis.

2. *Group developing hypertension during the course of the disease* (12 men and

5 women: 20 per cent.). All but three patients in this group had either chronic glomerulitis or healed renal polyarteritis; these three showed ischaemic changes in the kidneys, but only slight atheroma. This incidence of chronic lesions differs very significantly from that found in Group 1 ($\chi^2 = 19{\cdot}19$; $P < 0{\cdot}001$). Urinary abnormalities compatible with renal polyarteritis or glomerulitis preceded the appearance of hypertension in all the eight patients as to whom data were

TABLE XII

Incidence of various Renal Lesions at Necropsy, grouped according to Blood-Pressure during Life

	Group with normal blood-pressure (48 patients)		*Group developing hypertension (17 patients)*		*Group with initial hypertension (21 patients)*	
Necropsy findings	*Number*	*% of necropsy cases*	*Number*	*% of necropsy cases*	*Number*	*% of necropsy cases*
(Number of necropsies) .	(37)	(100)	(15)	(100)	(19)	(100)
Glomerulitis, initial phase .	17	46	1	7	2	11
Glomerulitis, chronic phase .	0	0	6	40	1	5
Polyarteritis, acute only .	20	54	0	0	2	11
Polyarteritis, healed . .	6	16	8	53	15	79
No chronic glomerulitis or healed polyarteritis . .	31	84	3	20	3*	16

* Renal polyarteritis proved at nephrectomy six years earlier in one of these patients.

adequate. The blood-pressure began to rise from six weeks to six months after the first evidence of renal involvement. At least four patients in this group developed malignant hypertension, the intervals from the first recorded rise in blood-pressure to the appearance of papilloedema being five weeks, seven weeks, six months, and four years. At necropsy one of them showed non-inflammatory arteriolar necroses, with the distribution typical of malignant hypertension.

3. *Group with hypertension at the initial examination* (13 men and eight women: 24 per cent.). Two of these patients were known to have had hypertension for at least two and three years respectively before the apparent onset of polyarteritis nodosa. In the remaining cases the blood-pressure was not recorded until two months to six years after the onset of the disease. Data regarding urinary findings were adequate in 18 patients, all but one of whom showed protein or red blood-cells at the first examination. The exception was one of the patients known to have pre-existing hypertension. Four patients had malignant hypertension at the time of admission to hospital, and five others developed it in hospital. In another four the blood-pressure rose progressively during the period of observation. At necropsy chronic glomerulitis or healed polyarteritis of renal arteries was found in all but three cases, and in one of these a kidney removed six years earlier had shown polyarteritic lesions. After the operation the patient had continued to pass protein and red blood-cells in the urine, so that it can be presumed that lesions were bilateral. His blood-pressure at the time was 160/110; shortly before his death from cerebral haemorrhage it had risen to 235/135. At necropsy the remaining kidney showed only hypertensive changes. It thus appears that the incidence of healed renal lesions in this group closely resembles that in Group 2, and once again there is a highly significant difference from Group 1 ($\chi^2 = 24{\cdot}33$, $P < 0{\cdot}001$).

Sex difference in the incidence of malignant hypertension. There was little difference between the two sexes in the total incidence of hypertension; it was present at some stage in 25 men (47 per cent.) and 13 women (39 per cent.). Malignant hypertension, however, occurred in 11 men (21 per cent.), but in only two women (six per cent.). A part at least of this difference may be due to the higher mortality among women early in the disease, before the stage at which malignant hypertension most frequently developed. The blood-pressure remained normal in only two women who survived six weeks or more from the first evidence of renal involvement. There was no difference in the incidence of renal polyarteritis (59 per cent. of men and 67 per cent. of women).

Hypertension in patients with lung involvement. In the first part of this paper a classification of polyarteritis nodosa was suggested on the basis of the presence or absence of lung involvement. The incidence of renal involvement was slightly higher in the group with lung involvement, but the average survival from the onset of renal lesions was shorter. The incidence of hypertension in this group was considerably less, probably as a result of their shorter survival: seven (23 per cent.) of the 31 patients with lung involvement and adequate data on blood-pressure had hypertension, as compared with 31 (56 per cent.) of the 55 patients with adequate data and no lung involvement.

Other features of the disease in patients with hypertension. At necropsy the various organs were involved with about the same frequency and severity in patients who had had hypertension and in those who had not. Healed lesions, however, were more frequent in the hypertensive group; in seven hypertensive patients necropsy revealed no active polyarteritis, whereas in all but one of those with normal blood-pressure there were recent lesions. Two other features which occurred more frequently in hypertensive patients were aneurysms and involvement of the medium-sized arteries.

Discussion

The renal findings at necropsy in cases with normal blood-pressure show that acute glomerular or arterial lesions do not cause hypertension, even when obstruction of glomerular capillaries or renal arteries is severe. This is surprising in view of the early rise in blood-pressure which occurs in ordinary acute glomerulonephritis. The presence of fever may have tended to lower the pressure in some cases, but sometimes severe renal involvement occurred with normal blood-pressure even in the absence of fever.

Observations on patients who developed hypertension during the course of the disease show that the pressure only started to rise after the appearance of proteinuria or haematuria, and that at necropsy 12 of the 15 patients in this group showed healed renal polyarteritis or glomerulitis, usually with infarcts or ischaemic fibrosis. The other three all had ischaemic fibrosis which, in the absence of more than slight atheroma, was probably due to renal polyarteritis. (The possibility that renal polyarteritis may no longer be demonstrable in the later stages of the disease is shown by the case, quoted earlier, in which lesions were found at nephrectomy but were not found in the remaining kidney at

necropsy six years later.) These necropsy findings contrast markedly with those recorded in the group with normal blood-pressure, in which healed polyarteritis with ischaemic fibrosis was seen only twice. These observations suggest that hypertension appearing during the course of polyarteritis nodosa is a sequel of renal polyarteritis or glomerulitis, but that the blood-pressure rises only during the healing stages of these lesions. The rate at which it rises is variable; but once initiated the rise is progressive, and in patients who survive long enough it is likely to terminate in the malignant phase. In this series, patients who developed hypertension had shown, in all instances where data were available, some initial rise of blood-pressure during the first few months of the illness; it remains to be seen whether the same will hold true of cortisone-treated patients. The presence of a high arterial pressure does not apparently aggravate the course of polyarteritis nodosa, since seven of the eight patients in whom no active polyarteritis was found at necropsy had had hypertension.

In the group of patients who had hypertension at the initial examination there was, in all but two cases, an interval of months or years between the onset of the disease and the first measurement of the blood-pressure. In the other two cases there was fairly good evidence that hypertension preceded the onset of polyarteritis nodosa; but this incidence of hypertension (2 per cent.) is no more than would be expected in a random sample of the population. In the other patients the relation between the high blood-pressure and the onset of polyarteritis nodosa was not clear; but there are three relevant observations. First, there was no evidence that hypertension ever preceded the appearance of urinary abnormalities compatible with renal polyarteritis nodosa; the urine already contained protein or red blood-cells when first examined. Secondly, in nearly half the cases there was evidence that hypertension was advancing rapidly. And lastly, the renal findings at necropsy closely resembled those in the group known to have developed hypertension during the course of the disease. It is suggested that no great weight can be attached to the evidence from patients in this group, in view of the delay before the blood-pressure was first measured; but the findings are consistent with the view that hypertension was secondary to renal involvement.

It thus seems extremely probable that, in nearly all cases of polyarteritis nodosa with hypertension, the high blood-pressure is not a precursor of the disease but a result of it. This is in strong contrast with the views expressed by Zeek and her colleagues (for example, Knowles, Zeek, and Blankenhorn, 1953). Unfortunately it is impossible to assess the adequacy of their data, since they did not state how early in the disease the blood-pressure was first measured, or mention serial recordings of blood-pressure. Apparently no patient either developed hypertension, or had a significant rise in blood-pressure, during the course of the disease. Such a finding is hard to reconcile with the observations of other workers, most of whom have considered the development of hypertension during the disease to be a very common occurrence (for example, Grant, 1940; Miller and Daley, 1946; Wold and Barker, 1949). The recognition of hypertension as a complication of polyarteritis nodosa is important, since in

some patients it may be the presenting feature. Polyarteritis nodosa should be considered as a possible diagnosis in all cases of severe or rapidly increasing hypertension associated with evidence either of a constitutional illness (loss of weight, fever, high blood sedimentation rate, or persistent leucocytosis), or of unexplained lesions in other systems. Muscle biopsy in such cases is fully justified. Less frequently such patients may first be seen after active polyarteritis has ceased. Recognition of the true cause of hypertension in such cases is obviously extremely difficult, and depends on obtaining a history of an earlier illness suggestive of polyarteritis nodosa. Diagnosis, however, is of real importance only when there is still active polyarteritis; in such cases it is probable that adequate cortisone treatment may prevent further renal damage, although it is doubtful whether it affects the advance of hypertension.

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We are grateful to the Collagen Diseases and Hypersensitivity Panel of the Medical Research Council for permission to publish these results. At the time of the survey one of us (G. A. R.) was employed on their behalf. A complete analysis of the series, together with the case histories, has been lodged with the Medical Research Council. A copy can be loaned on request.

The survey was made possible only through the generous co-operation of the clinicians, pathologists, and records officers of the various hospitals concerned who, without exception, gave the fullest assistance in providing access to the material from their cases. Cases were drawn from the following hospitals: Canadian Red Cross Memorial Hospital, Taplow (Special Unit for Juvenile Rheumatism); Guy's Hospital; Hammersmith Hospital and Postgraduate Medical School of London; the London Hospital; the Radcliffe Infirmary, Oxford; the Royal Infirmary, Edinburgh, and hospitals served by the Edinburgh University Department of Pathology; the Royal Infirmary, Manchester; St. Mary's Hospital; St. Thomas's Hospital.

We wish to offer sincere thanks to Professor G. W. Pickering for his constant interest and help. One of us (G. A. R.) wishes to record his indebtedness to Professor R. R. H. Lovell, who gave unstinted and invaluable advice; and also to thank Dr. R. T. Grant and Dr. W. I. Cranston for helpful comments and suggestions, and Miss J. E. Hollobon and his wife for secretarial assistance.

APPENDIX

The definition of hypertension used in this paper is based on the following figures for the expected blood-pressure in different age-groups of the population, taken from Hamilton, Pickering, Roberts, and Sowry (1954):

A. Male subjects

Age (years)	*Systolic pressure (mm. Hg)*	*Age (years)*	*Diastolic pressure (mm. Hg)*
10–15	115	10–13	65
16–30	120	14–25	70
31–39	125	26–38	75
40–44	130	39–51	80

Age (years)	*Systolic pressure (mm. Hg)*	*Age (years)*	*Diastolic pressure (mm. Hg)*
45–52	135	52–70	85
53–57	140	71–84	90
58–61	145		
62–65	150		
66–69	155		
70–73	160		
74–76	165		
77–79	170		
80–82	175		
B. Female subjects			
–31	120	–23	70
32–37	125	24–34	75
38–41	130	35–43	80
42–46	135	44–53	85
47–49	140	54–64	90
50–53	145	65–84	95
54–56	150		
57–60	155		
61–63	160		
64–66	165		
67–69	170		
70–72	175		
73–75	180		

Summary

A retrospective study has been made of 111 proven cases of polyarteritis nodosa which had been under care in nine teaching hospitals during the period 1946 to mid-1953. In seven patients the appearances were atypical; these were not considered further. The study provided new information particularly with regard to classification, aetiology, and blood-pressure changes.

It seemed that the most useful classification was one based on the presence or absence of lung involvement. Cases with lung involvement tended also to show a number of other features which were not seen, or were only rarely seen, in the other group. The chief of these were a respiratory illness initiating and generally dominating the disease, blood and tissue eosinophilia, granulomatous polyarteritis, and necrotizing lesions not demonstrably related to arteries. These features are described, and are contrasted with the findings in cases without lung involvement. The possible relation of the syndrome to other diseases is discussed, and some previous reports are reviewed.

The aetiology of the disease remains uncertain, but there is evidence of an association with preceding respiratory infections (especially those due to streptococci) and with rheumatic fever. Further investigation is needed to determine the relative importance of the infection and its treatment; at present the infection itself is chiefly suspect. In a few cases the disease appears to have been due to sensitivity to drugs of the thiouracil group; the evidence by which other drugs have been incriminated is weak.

An attempt was made to correlate blood-pressure changes with the urinary and necropsy findings in the 86 cases in which blood-pressure records were

adequate. (1) Among the 48 patients whose blood-pressure remained normal, recent renal polyarteritis and glomerulitis were common, but healed lesions were rare. (2) Of the 17 patients who were observed to develop hypertension during the course of the disease, all but three showed healed renal polyarteritis or glomerulitis at necropsy, and urinary abnormalities had preceded the first rise in pressure in all patients of whom data were adequate. (3) In 21 patients the blood-pressure was high when first measured, but in all but two the first record was made months or years after the onset of the disease; the necropsy findings were the same as in Group 2. It is concluded that the development of hypertension in polyarteritis nodosa is associated with the healing stages of renal polyarteritis or glomerulitis.

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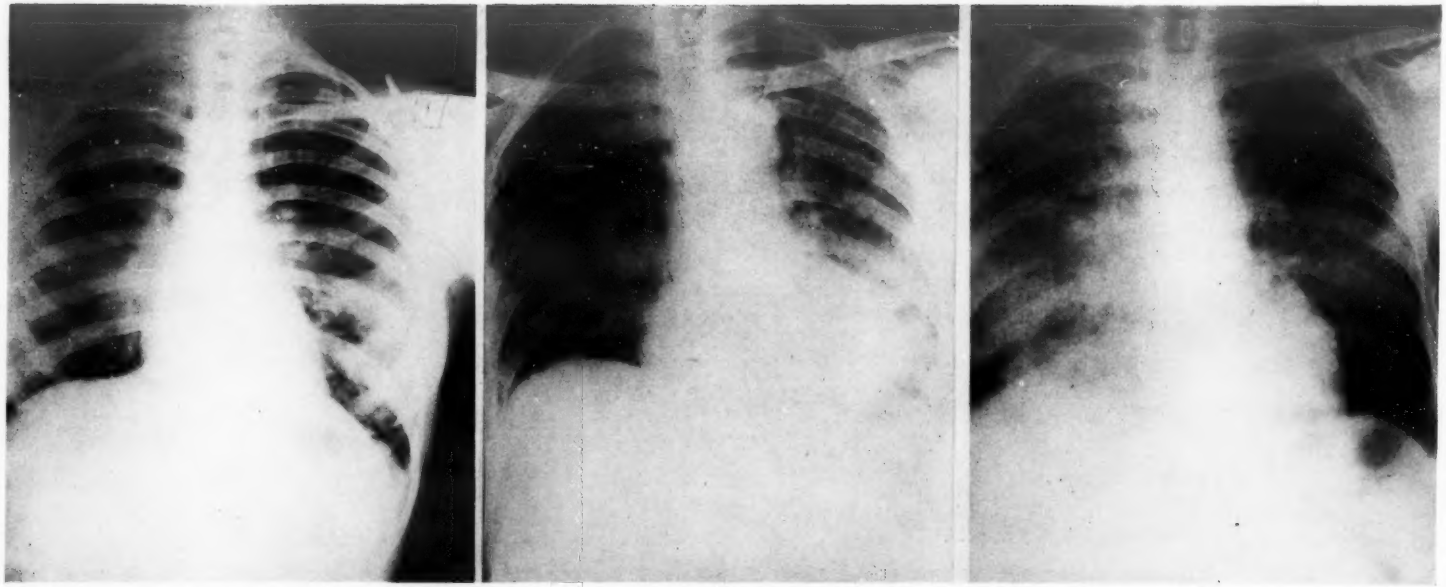
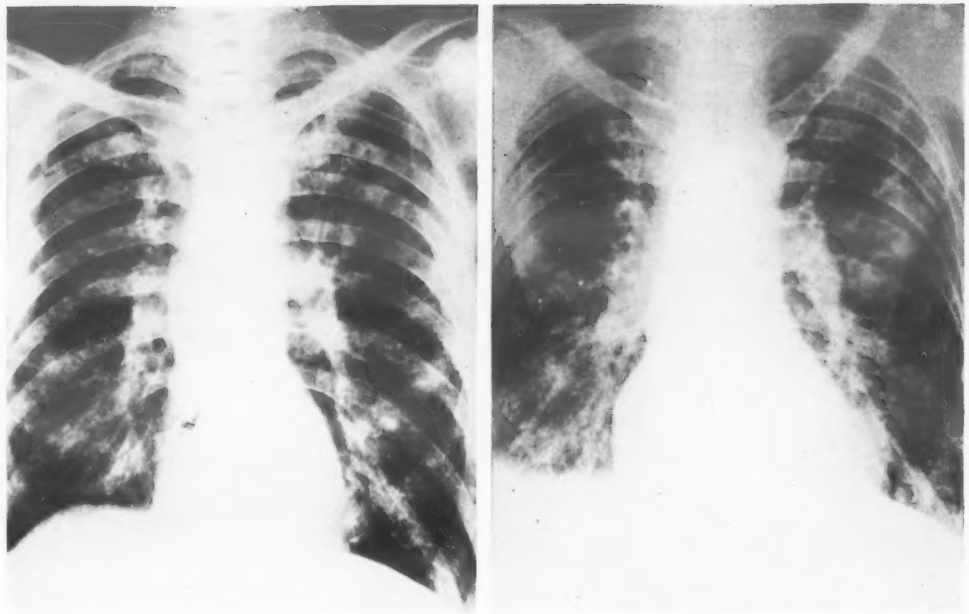


(a) (b)

FIG. 4. Infiltrations in the left lower zone and below the right hilum in a patient with asthma and high eosinophilia. Two weeks later the chest was radiologically normal (Case 73)

FIG. 5. (*a*) Widespread infiltrations, mainly in the left lung, with cardiac enlargement. (*b*) One month later there are extensive changes in the right lung; the left shows considerable resolution (Case 86)



(*a*) (*b*)

FIG. 6. (*a*) Bilateral discrete infiltrations and increased reticular pattern of the lung. (*b*) A film taken 17 months later shows, in general, progression of the lesions, although some on the left have cleared. The heart is much larger (Case 90)

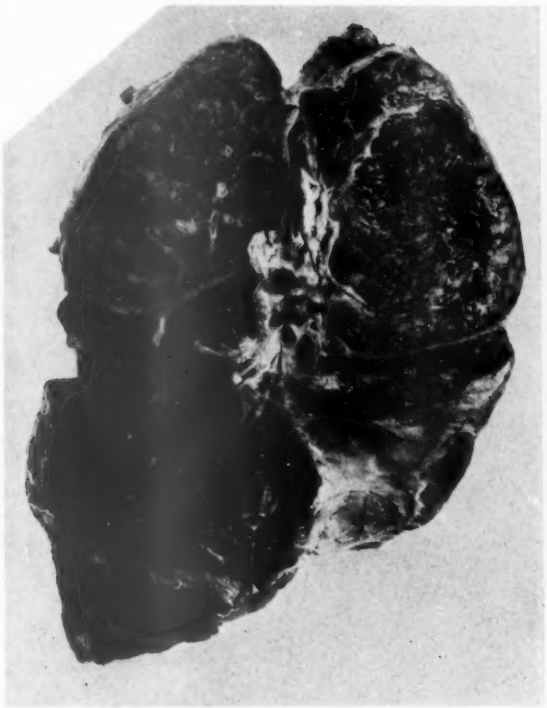


FIG. 7. Photograph of a lung, the upper lobe of which is largely necrotic and macroscopically resembles an unresolved pneumonia with a central abscess

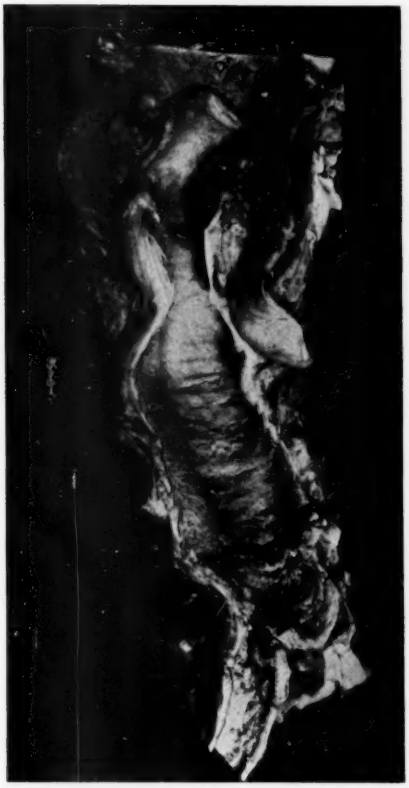


FIG. 8. Larynx and trachea, showing extensive ulceration of the latter. There were extensive necroses in the lungs

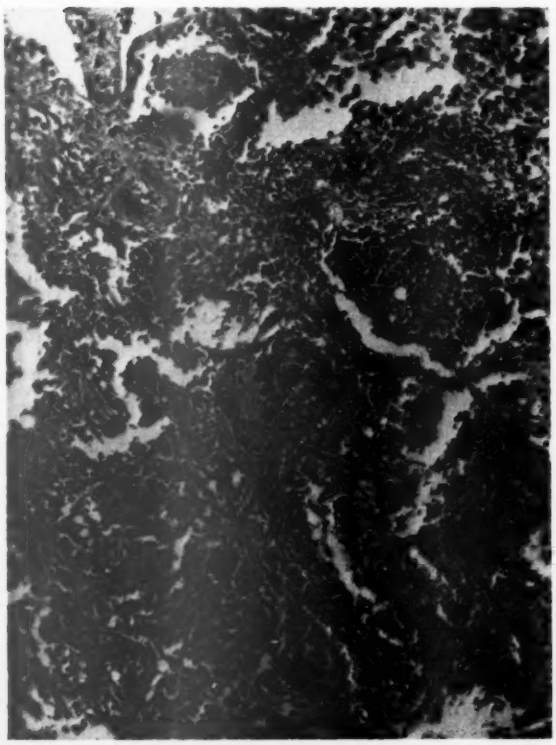


FIG. 9. Section of the necrotic area of lung in Fig. 7 showing a zone of complete destruction, with giant-cell reaction and many acute and chronic inflammatory cells at the margin of the necrotic area

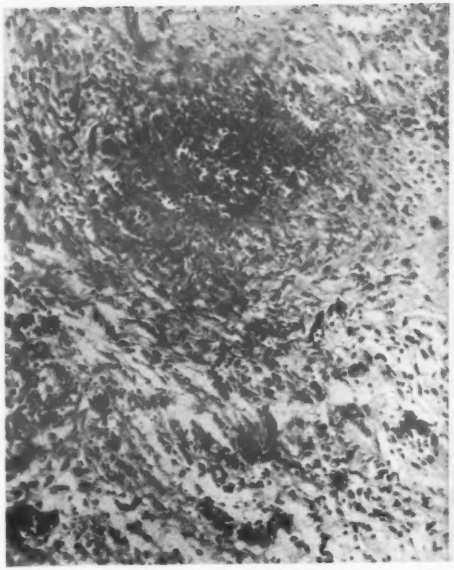


FIG. 10. A small focus of necrosis with surrounding fibrous tissue reaction. The more extensive lesions represent a confluence of these small areas of necrosis (×112)

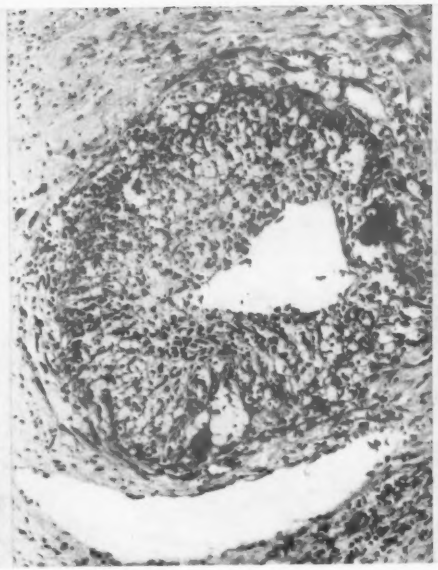


FIG. 11. An artery, containing acutely and chronically inflamed connective tissue and giant cells, lying immediately outside a necrotic area in the lung (×224)

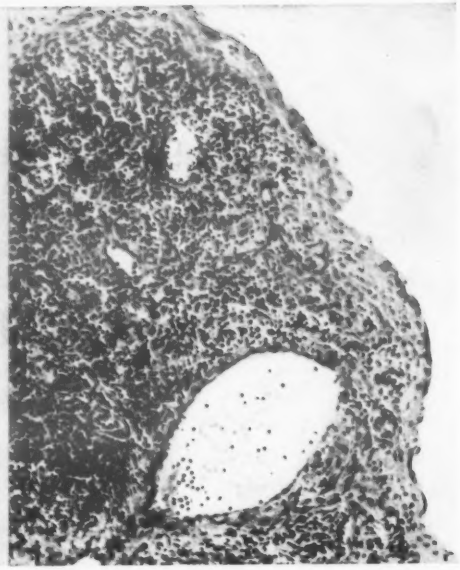


FIG. 12. Part of a nasal granuloma comprising large numbers of chronic inflammatory cells with a few polymorphs (×112)

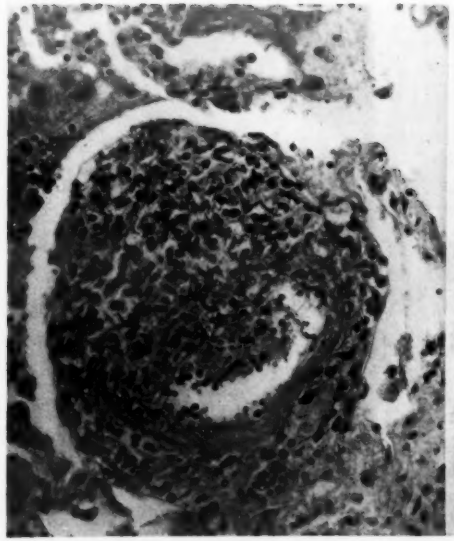


FIG. 13. Granulomatous polyarteritis showing absence of fibrinoid change and heavy cellular infiltration of a segment of the wall (×336)

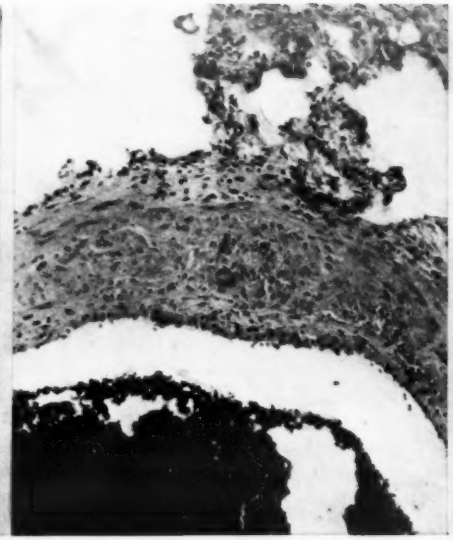


FIG. 14. Part of a superficial temporal artery from a patient showing generalized exudative polyarteritis. The intimal thickening with giant-cell reaction closely resembles the changes seen in giant-cell (temporal) arteritis (×224)

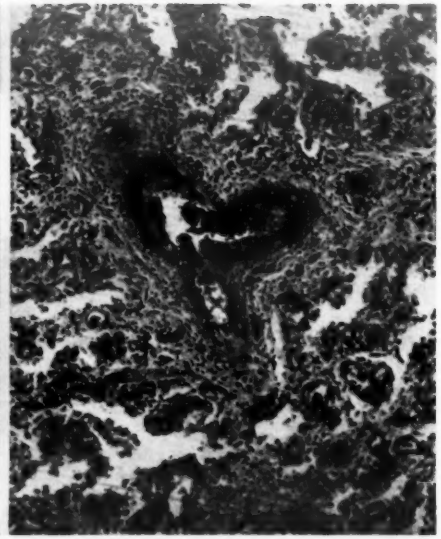


FIG. 15. Pulmonary arteritis associated with pulmonary hypertension due to mitral stenosis (×80)

616.131—008.333.1

UNEXPLAINED PULMONARY HYPERTENSION[1]

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With Plates 8 to 16

In 1891 Romberg reported a case in which hypertrophy of the right ventricle and pulmonary arterial sclerosis were found at autopsy in the absence of any apparent causal lesion, and during the next 50 years several further cases of unexplained right ventricular enlargement, with or without pulmonary arteriosclerosis, were reported. Although pulmonary arterial hypertension was suspected, the reported normality of the lungs in some of their patients led some workers to doubt this concept. Proof that pulmonary arterial hypertension may occur without apparent cause has been provided by cardiac catheterization, and several cases investigated in this way have been described. Adding three new cases, and reviewing 39 possible cases from the literature, Dresdale, Schultz, and Michtom (1951) first pointed out that the disorder, which they termed primary pulmonary hypertension, may be responsible for a distinctive clinical syndrome. They described this syndrome as generally occurring in young adults of either sex, with rapidly progressive symptoms due to a low cardiac output, and signs of pulmonary hypertension. They implied that there was a single aetiological entity, namely sympathetic overactivity. There is, however, some diversity, as regards both natural history and physical findings, in the cases reported under this diagnostic label. Even greater diversity exists in the reported histological findings in the lungs, and in their interpretation. Although Dresdale, Schultz, and Michtom (1951) implied that the lungs are often normal, and McKeown (1952) suggested that the term 'primary' pulmonary hypertension should be restricted to those cases in which the lungs are normal, other workers have described abnormal communications between the bronchial and pulmonary circulations (Brinton, 1950), diffuse occlusive lesions considered to be of embolic origin (Owen, Thomas, Castleman, and Bland, 1953), arteritic lesions (Berthrong and Cochran, 1955), primary persistence of foetal arteries (Goodale and Thomas, 1954), and the growth of intimal fibrous tissue into the pulmonary arteries from abnormal *Sperrarterien* (Könn, 1955).

In the present paper we report the findings in 10 cases of unexplained pulmonary hypertension, seven of which have been studied histologically. We

[1] Received June 11, 1956.

bring forward evidence that the cases are not homogeneous clinically or pathologically, and that two main mechanisms are concerned: (1) a functional contraction of the terminal muscular arteries, and (2) abnormal bronchopulmonary anastomotic channels. A third group may be required, distinguished from these by the presence of pulmonary arteritis. The clinical, haemodynamic, and pathological data are summarized in Tables I, II, and III.

TABLE I

Clinical Data

Case number	*Age (years)*	*Sex*	*Duration of disease*	*Dyspnoea*	*Fatigue*	*Effort syncope*	*Angina*	*Haemoptysis*	*Cyanosis*	*Cause of death*	*Differential agglutination test*	*Remarks*
1	11	F	17 mths.	+	0	+	0	0	0	A.R.V.F.	Negative	
2	36	F	18 mths.	+	+	0	0	0	Trace	C.H.F.	..	
3	14	F	10 mths.	+	0	+	0	0	0	A.R.V.F.	Negative	
4	37	F	12 mths.	+	0	0	0	0	+	C.H.F.	Negative	
5	40	F	?	+	+	0	+	0	0	..	Negative	Still alive
6	33	M	24 mths.	+	+	+	+	0	Trace	C.H.F.	Positive	
7	28	F	23 mths.	+	+	0	0	0	0	A.R.V.F.	Negative	Raynaud's phenomenon
8	27	F	?	+	0	0	0	0	0	..	Positive	Still alive. Raynaud's phenomenon
9	37	M	'Years'	+	0	0	0	+	+	Haemoptysis	Positive	
10	23	M	24 mths.	+	+	0	0	+	+	After operation	..	

A.R.V.F. = Acute right ventricular failure.
C.H.F. = Congestive heart failure.

Patients Investigated and Methods

Clinical. The 10 patients forming the basis of this study attended the Department of Cardiology at the Manchester Royal Infirmary during a period of three years, but the cases are not presented in chronological order. All, with the exception of Case 10, were personally interrogated and submitted to routine clinical and radiological examination, the physical and radiological findings being analysed after the manner of Wade, Werkö, Eliasch, Gidlund, and Lagerlöf (1952). Cardiac murmurs were graded after the classification of Levine and Harvey (1949). In all cases the usual investigations were carried out, including blood counts and the Wassermann reaction, and an electrocardiographic study made, consisting of the bipolar and unipolar limb leads and six precordial leads in the positions 1 to 6 using the central terminal of Wilson. In eight cases the differential agglutination test introduced by Rose, Ragan, Pearce, and Lipman (1948) was performed, using the method of Ball (1952); the reaction was regarded as positive if agglutination occurred in serum dilutions of 1:32 or higher. Eight patients were subjected to cardiac catheterization, which was performed in the usual manner; pressures were recorded with either a saline or a capacitance manometer, and referred to 5 cm. below the sternal notch, and blood gases were determined in duplicate, either with the Van Slyke-Neill manometric apparatus or with the Haldane apparatus as modified by Courtice

and Douglas (1946–7). Eight of the 10 patients are dead, and a post-mortem examination was made in seven.

Pathological. Except in Cases 1 and 10 the right ventricle and the left ventricle with attached septum were weighed separately, according to the method of Fulton, Hutchinson, and Jones (1952). The larger pulmonary arteries were

TABLE II

Haemodynamic Findings in Eight Patients Catheterized

Case number	*Pulmonary artery mean pressure (mm. Hg)*	*Pulmonary artery oxygen saturation %*	*Systemic blood-pressure*		*Brachial artery oxygen saturation %*	*Brachial artery oxygen saturation % on effort*	*Arteriovenous oxygen difference (vols. %)*
			Systolic	*Diastolic*			
1	68	51	110	60	94	94	7·0
2	55 (R.V.)	37	120	80	87	..	11·0
3	>78	43	110	85	87	92	8·5
4	>78	65	130	90	87	90	6·4
5	37	72	100	60	94	95	4·3
6	59	44	120	95	89	91	7·5
8	48	41	110	80	87	..	8·1
9	>78	..	120	70	..	..	..

examined by opening up the vessels, and the aorta and hilar region were inspected for evidence of abnormalities of the bronchial arteries. With the exception of Case 10, in which several lung blocks from unknown sites were available, the general distribution of pulmonary lesions was determined by a survey of single sections taken from blocks removed from the upper, middle, and lower zones of each lung. One or more of these blocks were then cut serially. The serial sections were found to be indispensable; in each case pulmonary arteries were found which could be traced to their terminations, and thus both the identity of the smaller vessels, which is often uncertain in casual sections, and the sequential pattern of morphological changes, could be determined with reasonable certainty. With occasional exceptions, each section in the series was stained successively with Weigert's elastic-tissue stain, haematoxylin, and van Gieson's stain for muscle and connective tissue; other stains such as haemalum and eosin, Gram's stain for bacteria, the periodic-acid-Schiff method, or Lillie's silver method for reticular tissue, were used when indicated. All measurements were made with an ocular micrometer. The terms 'external diameter' and 'internal diameter' refer to the average of two measurements of diameters delineated by the external and internal elastic membrane respectively. The cross-sectional area of the circular media of pulmonary arteries was derived by difference from the areas enclosed by the internal and external elastic membranes.

TABLE III

Pathological Findings in the Seven Cases in which Autopsy was performed

Case number		1	2	3	6	7	9	10
Sex and age (years)		F 11	F 36	F 14	M 33	F 28	M 37	M 23
Heart weight (gm.)	Total	330	305	345	405	..	700	680
	Left ventricle + septum	..	105	140	157	127	235	..
	Right ventricle	..	85	103	90	104	182	..
Pulmonary arteries	External longitudinal muscle (medial hypertrophy)	+	++	+++	+	+	−	−
	Thrombosis	−	+(all recent)	+(recent and old)	+	+(rare)	+(all recent)	−
	Intimal fibroelastosis	−	+	+	+	+(concentric)	−	−
	Medial defects	−	+	+	+(rare)	+(rare)	−	−
	Arteritis	−	−	−	+	+(mild, rare)	+(rare, healed)	−
	External diameter 40–80 μ	+	+	+	−	+	−	−
Terminal pulmonary arterioles		Normal	Normal	Normal	Arteriolitis	Normal	Normal	Normal
Alveoli		Normal	Normal	Normal	Normal	Rare focal alveolar fibrosis	Normal	Normal
Bronchopulmonary anastomoses		−	−	−	−	−	+	+
Bronchial arteries		Normal	Normal	Normal	Normal	Normal	Hypertrophied	Hypertrophied
Arteritis (extra-pulmonary)		−	..	−	−	+	−	−

None of the patients had rheumatic or congenital heart disease, except for Case 7, in which there was a small atrial septal defect.

The lumen/wall-thickness ratio or the wall-thickness/external diameter ratio in pulmonary arteries is sometimes quoted, as a measure of either medial hypertrophy or constriction of the lumen, or both (Brenner, 1935; Larrabee, Parker, and Edwards, 1949; Heath and Whitaker, 1955*a*). These ratios, however, do not remain constant with varying overall diameters of a given vessel, and hence cannot of themselves distinguish between medial thickening due to hypertrophy and that due to constriction of the vessel as a whole. In the present paper the diagnosis of medial hypertrophy is based largely on a qualitative change, namely the occurrence of longitudinal or spiral muscle in pulmonary arteries; and evidence of vascular constriction has been adduced by comparing the cross-sectional area of the media in hypertensive and control cases. With the reasonable assumptions of a constant muscle volume and insignificant changes in length during contraction, the cross-sectional area remains constant at varying overall diameters. Hence a variation in diameter for a given cross-sectional area is a measure of variation in length of the circular muscle-fibres in the artery wall.

Histological Considerations

The normal histological structure of the pulmonary and bronchial vessels was studied in 107 lung sections from routine necropsy in 77 subjects who died of a variety of diseases; all were selected on the basis of a normal heart. With certain reservations mentioned below, the validity of Brenner's (1935) scheme of dividing the pulmonary artery system into four structural segments has been confirmed and adopted in the present paper, and for clarity and convenience the salient points of the scheme are reproduced here.

1. *Elastic arteries.* These vessels have an external diameter usually greater than 1,000μ. Their walls contain numerous elastic lamellae as well as smooth muscle.
2. *Muscular arteries* have a media composed of circular muscular fibres delineated by an internal and external elastic membrane. They range from about 1,000μ to 100μ in diameter.
3. *Arterioles* are non-muscular vessels, usually less than 100μ in diameter, whose wall consists of an endothelial layer supported by a single elastic membrane.
4. *Capillaries* have neither muscle nor elastic tissue in their walls, the endothelium being supported by a fine basement membrane only.

The point at which muscle-fibres disappear from the pulmonary artery system has a special relevance, because of the occurrence of muscular arteries 60μ or less in diameter in some of the cases described below: Table IV shows the external diameter of the smallest artery with a well-defined media found in the 77 control cases. It will be seen that muscular arteries less than 60μ in diameter were characteristically present in all newborn lungs, but were found in only two of the remaining 69 cases, and both of these patients were aged under two years. Muscular vessels between 80 and 60μ were rare, and in each

case vessels of this order were the exception rather than the rule. These findings are in accord with the observations of Civin and Edwards (1951); and it may be asserted that in subjects over the age of five years muscular pulmonary arteries have, in general, an external diameter not less than about 80μ. It should also be stressed that the pre-capillary pulmonary arteriole is a non-muscular vessel, and hence presumably incapable of active contraction.

TABLE IV

External Diameter of the Smallest Muscular Arteries seen in 77 Normal Control Cases in Various Age-groups

Age	*External diameter of smallest muscular artery*			*Total*
	> 80 μ	79–60 μ	< 60 μ	
New-born. . .	0	0	8	8
10 months–5 years .	1	3	2	6
6–15 years . .	11	2	0	13
16–25 years . .	10	3	0	13
26 years and over .	35	2	0	37

The bronchial arteries are very much smaller than the neighbouring pulmonary artery, and are for the most part confined to the bronchial wall. They are tortuous and, unlike the pulmonary artery, make frequent anastomoses. According to Miller (1947) they terminate in a capillary plexus in the walls of respiratory bronchioles. Verloop (1948) and Parvis (1953–4) have shown that the bronchial arteries possess a longitudinal muscle layer lying internal to the circular muscle coat. This longitudinal layer may be only one or two cells thick, or may account for most of the wall thickness, in which case the lumen is usually found to be minute, or even apparently completely closed. Such vessels have been called *Sperrarterien*, and most observers have assumed that this peculiar structural arrangement affords a means of controlling local blood-flow (von Hayek, 1953; Parvis, 1953–4), but no convincing evidence of this mechanism is available. Miller (1947) denied the existence of pre-capillary bronchopulmonary arterial anastomoses, but more recent workers claim to have shown that, in the region of small cartilaginous bronchi, short tortuous branches of the bronchial arteries normally run distally to form anastomoses with branches of the neighbouring pulmonary artery. These anastomotic vessels have the typical structure of *Sperrarterien* (von Hayek, 1953; Verloop, 1948; Tobin, 1952). Although the bronchial arteries are normally distinguishable from the pulmonary arteries by their size, structure and position, the method of tracing out the pulmonary arteries to their termination in the alveolar bed avoids their confusion, which might arise in pathological lungs, with bronchial arteries.

Case Reports

Case 1. P. B., an 11-year-old schoolgirl, was admitted to the Royal Infirmary on 24.10.54. She had enjoyed excellent health until, in July 1953, she suddenly collapsed during a game; she was unconscious for about a minute. From about this time onward she experienced increasingly severe dyspnoea on effort, and in

August had a further syncopal attack on exertion. In September 1953 the school doctor discovered a heart murmur, and in the same month her parents noticed that her chest heaved with each heart beat. In April 1954 she was seen by a consultant paediatrician, who confirmed the presence of a heart murmur but did not think there was any cardiac disease. In July 1954 she developed oedema of the ankles and face; this was regarded as of renal origin, and subsided

TABLE V

The Effect upon Circulatory Dynamics in Case 1 of Exercise, Hexamethonium Bromide, and Tolazoline

State	Drug	Route	Dose (mg.)	Pulse-rate	Oxygen consumption (ml./min.)	Brachial artery oxygen content (vols. %)	Pulmonary artery oxygen content (vols. %)	Arteriovenous oxygen difference (vols. %)	Cardiac output (l./min.)	Systemic blood-pressure (mm. Hg)		Pulmonary artery pressure (mm. Hg)			Total pulmonary resistance (c.g.s. units)
										Systolic	Diastolic	Systolic	Diastolic	Mean	
Basal	Nil	..	..	94	109	17·6	10·6	7·0	1·6	90	70	93	46	68	3,140
Ex.	Nil	..	..	120	235	17·6	7·75	9·85	2·4	..	..	110	56	79	2,460
Rest	C_6	Intravenous	5	96	140	17·6	9·2	8·4	1·7	70	..	..	..	69	3,010
Rest	Tolazoline: 2 minutes after	Intravenous	15	110	..	..	11·9	..	..	150	95	..	..	59	..
	4 minutes after	..	..	..	..	..	..	..	..	..	..	..	..	63	..

C_6 = hexamethonium bromide. Ex. = exercise.

after five weeks in bed. Oedema recurred in September 1954, and she was admitted on account of this.

On examination she was well-developed, with a malar flush, but not cyanotic. There was a parasternal heave, a grade II pulmonary systolic murmur, great accentuation of the pulmonary second sound, and a grade II apical systolic murmur. The neck veins were distended, the liver was enlarged three finger-breadths below the costal margin, and there was ascites. The blood-pressure was 100/70. Other systems were normal. Fluoroscopy showed great enlargement of the right ventricle and proximal dilatation of the pulmonary arterial tree. Electrocardiography showed extreme right ventricular hypertrophy. A blood count showed red cells 5,400,000 per c.mm., and haemoglobin 116 per cent. The differential agglutination test was negative, serum-albumin 4·3 gm., serum-globulin 2·9 gm. per 100 ml., and renal function tests normal. L.E. cells were not found. Urinary noradrenalin was normal. Cardiac catheterization showed a mean pulmonary artery pressure of 68 mm. Hg, with an oxygen saturation of 51 per cent., and no shunt.

This patient was catheterized twice. On the first occasion the effects of exercise were studied, and on the second the effects of hexamethonium bromide and tolazoline. It was found that effort, although causing a rise in pulmonary arterial pressure from 68 to 79 mm. Hg, produced a slight fall in total pulmonary resistance, from 3,140 to 2,460 units (Table V). The rise in output was small (1·6 to 2·4 litres per minute), and the increase in oxygen consumption was largely met by greater utilization. Hexamethonium bromide was without effect, but the injection of 15 mg. of tolazoline into the catheter caused a fall of 10 mm. Hg in pulmonary arterial pressure, and a rise in pulmonary arterial oxygen content from 9·2 to 11·9 vols. per cent. There seems to be little doubt that resistance to blood-flow through the lungs was diminished, but the effects were so transient

that no output estimations could be made. She was treated for heart failure with good effect, and also given oral tolazoline, 25 mg. every three hours. On 27.11.54 she suddenly collapsed and died of acute circulatory failure.

Post-mortem macroscopic findings

The external appearances were normal for an 11-year-old girl. The heart (330 gm.) was enlarged owing to an isolated right ventricular hypertrophy, this chamber being dilated and its anterior wall 6 to 7 mm. thick at a point one inch below the pulmonary valve. The wall of the pulmonary artery stem and extra-pulmonary branches appeared thicker than normal, but their internal surfaces were smooth and free from atheroma. The heart and great vessels were otherwise normal, apart from a slight excess of pericardial fluid.

Lungs. Each pleural cavity contained about 300 ml. of clear amber fluid, but the pleurae were normal. On section no abnormality was detected apart from slight prominence of the pulmonary arteries, in which small yellowish intimal plaques or streaks were scattered here and there in most branches down to 2 or 3 mm. in size. In contrast the thoracic aorta was virtually free from atheroma. There were no thrombi.

Other viscera. Some passive congestion was noted in the liver, kidney, and spleen, and the abdominal cavity contained about half a litre of blood-tinged fluid, the peritoneal surface being apparently normal.

Microscopic findings

Lungs. Apart from slight congestion and oedema in the lower zones, the appearances were essentially the same throughout both lungs. Elastic arteries were mildly atheromatous, and showed moderate degrees of cystic medial necrosis. In muscular arteries the media appeared thicker than normal, and the elastic membranes were wrinkled. This impression was confirmed by the observation that the external diameter/wall-thickness ratio in 15 arteries measuring 216 to 110 μ in diameter (mean 148 μ) was 10 (range 7 to 19) as compared with 26 (range 6 to 54) in 28 control vessels measuring 240 to 120 μ (mean 160 μ). Occasionally the circular media was supplemented by longitudinal or spiral muscle-bundles, lying external to the circular coat and sometimes delineated by an extra elastic membrane (Plate 8, Fig. 1). These external muscle-bundles were found in arteries as small as 200 μ, but not in smaller vessels; they are considered to be good evidence of muscle growth at this level, since they are most inconspicuous or not seen at all in normal lungs. The intima was normal in muscular arteries larger than 150 μ. In some smaller arteries the intima contained longitudinal muscle-fibres (see below), but other forms of intimal thickening were never seen. There was no trace of arterial, arteriolar, or venous thrombosis.

The most interesting histological abnormality was the presence of a circular media in pulmonary arteries 80 to 40 μ in diameter, in which the endothelium was normal and the elastic membranes prominent and wrinkled (Plate 8, Figs. 2*a*, *b*). These abnormally small muscular pulmonary arteries invariably joined arterioles about 60 μ in diameter, which in turn supplied the alveolar bed. The short junctional area of abnormally small arteries and arterioles was often straddled by bundles of longitudinal smooth muscle, forming an incomplete layer between normal endothelial cells and the internal elastic membrane (Plate 8, Fig. 2*c*). The muscular nature of the intimal proliferations (which were more highly organized in arteries than in arterioles) was deduced from the observations that they were fibrillar, birefringent in polarized light, stained with the picric acid in the van Gieson stain, sparsely populated with typical muscle

nuclei, and often provided with a reticular framework stainable with the periodic-acid-Schiff method. It should be stressed that this intimal growth was strictly confined to the region where artery and arteriole joined, and that the terminal arteriolar segment was, without exception, structurally normal (Plate 8, Figs. 3 and 4). The termination of the pulmonary artery tree was thus characterized by abnormally small muscular vessels, normal terminal arterioles,

TABLE VI

The Cross-sectional Areas and External Diameters of Small Muscular Pulmonary Arteries in Case 1 and in Control Subjects of Similar Age

	Number of arteries	*External diameter (μ)*		*Cross-sectional area of media (μ²)*	
		Range	*Mean*	*Range*	*Mean*
Case 1 . .	15	38–62	50	453–1,499	949
Controls .	13	87–112	99	553–1,572	1,005

and a normal capillary bed. This structural sequence was found in every pulmonary artery followed in serial section, and, once recognized, it was readily observed in sections from all parts of both lungs. There was one exception to this rule; the occasional arteriole which normally arises at right angles from large muscular arteries showed only narrowing of the lumen by a non-fibrous intimal hypertrophy similar to that seen in distal arterioles; in these branches, therefore, there was no abnormally small artery interposed between the parent vessels and the arteriole.

The possibility was considered that the abnormally small pulmonary arteries merely represented contracted but otherwise normal vessels. It was tested by comparing the cross-sectional area of the circular media of these vessels (choosing those in which internal longitudinal muscle was absent or inconspicuous) with values obtained in small muscular pulmonary arteries in young subjects in whom there was no cardiac or pulmonary condition likely to be associated with pulmonary hypertension. The results are shown in Table VI, where it will be seen that in Case 1 the mean cross-sectional area, in arteries with a mean external diameter of 50 μ, is not significantly different from that of control arteries of about twice this size. The mean cross-sectional area in the controls is closely similar to that given by O'Neal, Thomas, and Hartroft (1955) for normal pulmonary arteries of comparable size. It is thus possible that the terminal muscular arteries of a normal lung would, if actively contracted to about half their size, assume the appearance of the abnormally small arteries found in the present case; and the constant occurrence of wrinkled elastic membranes and a prominent adventitia in these vessels favours this interpretation.

Some alveolar congestion and oedema was present, mainly in the basal zones, but in general the alveolar capillaries were normal, and there was a notable absence of recent or old alveolar, interstitial, or perivascular inflammation. Anastomoses between bronchial and pulmonary arteries, or pulmonary arteries and veins, were not seen. The pulmonary veins appeared normal.

Other viscera. The left auricle and ventricle presented no abnormality; the right ventricle showed only myocardial hypertrophy. Apart from passive congestion, the liver, spleen, pancreas, and intestine were within normal limits.

Comment. The history is short and progressive. The main symptoms of dyspnoea and syncope on effort suggest a limited cardiac output. The duration of the hypertension is uncertain, but the parents did not observe a heaving

impulse until some two months after the onset of symptoms. The precise mode of death is uncertain; presumably it was due to acute failure of the right ventricle. The presence of external longitudinal muscle-bundles in pulmonary arteries about 200μ in diameter is good qualitative evidence of muscle growth; and if it is allowed that this is a work hypertrophy, the increased resistance to blood-flow was probably located between this point and the structurally normal arteriole supplying the normal capillary bed. In this segment of the pulmonary artery tree the most constant abnormality was the presence of unusually small muscular arteries, similar to those normally found in foetal lungs, but having thicker elastic membranes. It is unlikely that they were a post-mortem artefact, for vessels of this type are rarely seen in normal lungs (Table IV). It is difficult to believe that the abnormally small muscular arteries are a structural adaptation to hypertension, for the vessels distal to them, namely normal arterioles, are, on morphological grounds at least, incapable of active resistance to blood-flow. Measurements of the cross-sectional areas of the media in these small vessels suggest they may be merely contracted terminal arteries, and we consider this the most probable explanation of the increased hindrance. The intimal longitudinal muscle could hardly be the cause of their small size, since its contraction would tend to increase rather than decrease the external diameter of the vessel in which it occurs. The primary cause of the active vasocontraction of the terminal muscular arteries is unknown. It was unaffected by hexamethonium bromide, and therefore was presumably not due to sympathetic overactivity. There is a suggestion that the adrenolytic substance, tolazoline, caused vasodilatation (although simultaneous values for cardiac output were not obtained), but the urinary content of pressor amines was not increased.

Case 2. M. B., a 36-year-old housewife, was admitted to the Royal Infirmary on 28.10.52. She had always enjoyed good health, apart from pre-eclampsia complicating her only pregnancy seven years previously. Towards the end of 1950, after an attack of infective hepatitis, she became aware of dyspnoea on effort, associated with muscular fatigue. These symptoms progressed, and in April 1952 she developed swelling of the ankles and, later, the abdomen. During 1952 she suffered five syncopal attacks unrelated to exertion and usually accompanied by vomiting. An electrocardiogram taken in June 1952 showed right ventricular hypertrophy.

Examination showed moderate cyanosis and icterus, a parasternal heave, a grade I pulmonary systolic murmur, and gross accentuation of the pulmonary second sound. The blood-pressure was 120/80. There were signs of congestive heart failure. An X-ray showed great enlargement of the right ventricle, and proximal dilatation of the pulmonary arterial tree. Electrocardiography showed extreme right ventricular enlargement. Red blood-cells were 5,770,000 per c.mm., haemoglobin 112 per cent., serum-bilirubin 2·3 mg. per 100 ml., and urea clearance 73 per cent. of normal. Cardiac catheterization showed a mean right ventricular pressure of 55 mm. Hg, and an oxygen saturation of 38 per cent.; the pulmonary artery was not entered; no shunt was demonstrated. The systemic arterial oxygen saturation was 87 per cent. L.E. cells were not found in the peripheral blood. She was thought to have an atrial septal defect complicated by pulmonary hypertension and a reversed shunt, and was treated for heart

failure, but without avail, death occurring in January 1953. A limited post-mortem examination was made of the heart, lungs, and great vessels.

Post-mortem macroscopic findings

Lungs. The main pulmonary arteries at the hilum were atheromatous, and contained recent thrombi. Fibrous adhesions covered most of the pleural surface of the right lung posteriorly; the left pleural surface was normal. There were unduly prominent pulmonary arteries on the cut surface of the lungs, and many of the larger branches contained recent thrombi, but there was no evidence of infarction, emphysema, or inflammatory changes in the parenchyma.

The *Heart* (305 gm.) presented no abnormality apart from an isolated right ventricular hypertrophy; the right ventricle weighed 85 gm., the left ventricle and septum together 105 gm. No anatomical anomaly was found in the great vessels.

Microscopic findings

Lungs. The histological appearances had three features in common with the previous case. First, the pulmonary veins were normal, and the alveolar capillary bed showed no evidence of chronic congestion or fibrosis. Secondly, external longitudinal muscle-bundles were present in the muscular arteries (Plate 9, Fig. 5). Thirdly, pulmonary vessels (50 to 80 μ) with a well-defined media were present throughout (Plate 9, Fig. 6) and, as in Case 1, they always joined normal arterioles, the junctional zone showing degrees of intimal thickening, containing longitudinal muscle-fibres, which often caused marked reduction of the lumen. The terminal segments of the pulmonary artery tree thus presented the structural sequence already described in the previous case.

In contrast to Case 1, the muscular pulmonary arteries frequently contained medial defects and intimal fibrous or fibroelastic proliferations; pulmonary artery thromboses had also occurred. Medial defects usually involved a small part of the circumference at the origin of a branch, and here the two elastic membranes joined to form a single layer, the circular muscle at this point being hypoplastic or absent. An irregular area of intimal proliferation, variously composed of fibrous, elastic, and muscular tissue, frequently covered the defect, but sometimes the intima was normal. Occasionally the intimal proliferation was localized to the defect, but usually it formed part of the intimal sclerosis present in most of the muscular arteries and largely confined to branching sites. There was a notable absence of dilatation at the site of these medial defects (Plate 10, Fig. 9). In the larger branches the intimal sclerosis was mainly fibrous or fibroelastic, and never produced severe narrowing of the lumen; but in the smaller branches, down to vessels about 100 μ in diameter, the resulting obstruction, though variable, was often considerable. As mentioned above, the intimal proliferation in arteries 100 μ or less in diameter was predominantly muscular rather than fibroelastic. The intima of terminal arterioles was normal. Thrombi were found frequently in elastic arteries, occasionally in large muscular arteries, and very rarely in small arteries or arterioles. In small arteries the thrombus was often contained in a short dilated segment at the origin of a branch (Plate 10, Figs. 7 and 8). The larger vessels containing thrombi were also relatively thin-walled, and might also have been dilated. All thrombi were obviously of recent origin, and Fig. 8 illustrates the most advanced degree of organization encountered. The typical appearances of a fully organized and recanalized thrombus were not seen.

Comment. The patient's history is similar in many ways to that of Case 1. The symptoms are compatible with a low cardiac output, and the high degree

of unsaturation of the mixed venous blood supports this concept. We do not know the duration of the hypertension; no examination was made until 18 months after the onset of symptoms, and there was then evidence of right ventricular hypertrophy. There was more cyanosis than in the previous case, and we suggest that the unusual degree of cyanosis may have been due to the widespread but recent thromboses in the pulmonary arteries. In addition to abnormally small arteries joining normal arterioles—the structural sequence characterizing Case 1—there were in this case medial defects, intimal fibrosis, and thrombi. The relation of these added features to the hypertension must be considered. Medial defects occur in pulmonary and systemic arteries in normotensive states, and are not known to be associated with vasospasm; furthermore, in systemic arteries they are not a source of weakness, and do not predispose to intimal sclerosis (Glynn, 1940). In the present case intimal fibrosis usually produced only minor contraction of the lumen, and its association with medial defects may be merely coincidental, in that both tend to occur at branching sites. All the thrombi were of recent origin, and therefore unlikely to have been the cause of the hypertension. They were relatively rare in abnormally small arteries, and when present were contained in a conspicuously dilated segment of the vessel; moreover, the intimal longitudinal muscle in these arteries was probably not of thrombotic origin, for the organization of thrombi or emboli does not produce this type of structure. It is unlikely, therefore, that thrombosis was the cause of the abnormally small size or the intimal change in the terminal arteries. The cause of the thrombosis is obscure, and it is difficult to be certain whether the thrombi were autochthonous or embolic.

There is thus no sound reason for suggesting that either thrombosis or intimal changes could be primarily responsible for the hypertension. The findings are, however, compatible with the view that the basic mechanism was similar to that of Case 1, namely a contraction of terminal pulmonary arteries, the additional features being secondary phenomena.

Case 3. W. J., a 14-year-old schoolgirl, was admitted to the Royal Infirmary on 7.10.53. In January 1953, while running home from school, she first noticed dyspnoea, with substernal oppression and a feeling of faintness. On reaching home she collapsed, and was unconscious for about five minutes. These attacks became more frequent and more easily induced until the time of her admission. In some she was incontinent of urine and faeces, and she occasionally remained unconscious for as long as one hour. In August epilepsy was diagnosed, and appropriate treatment instituted, but with no benefit. Before the onset of symptoms she had enjoyed the best of health.

On examination she was a well-developed girl, without cyanosis. There was a parasternal heave, great accentuation of the pulmonary second sound, a grade II pulmonary systolic murmur, and a protodiastolic third sound. The blood-pressure was 110/85. Other systems were entirely normal. Fluoroscopy showed moderate enlargement of the right ventricle and proximal dilatation of the pulmonary arterial tree. Electrocardiography showed extreme right ventricular enlargement. Red blood-cells were 4,900,000 per c.mm., haemoglobin 98 per cent., and the differential agglutination test negative. Cardiac catheterization showed a mean pulmonary artery pressure exceeding 78 mm. Hg, with

an oxygen saturation of 43 per cent., and no shunt. Systemic oxygen saturation was 87 per cent. at rest, rising to 92 per cent. on effort. On 16.10.53, five minutes after performing an exercise test consisting of ascending and descending 36 eight-inch steps in one and a half minutes, she collapsed, becoming pale, cyanotic, and then comatose. Both pulse and blood-pressure were unobtainable. After administration of pressor amines she recovered sufficiently to complain of pain in the chest, but collapsed again, and died within 20 minutes.

Post-mortem macroscopic findings

Externally the body was normal for a girl of 14 years. The abdomen and thorax contained small quantities of clear yellowish fluid, but the serous surfaces were normal. The heart (345 gm.) and great vessels were normal apart from a thickened and dilated pulmonary artery and isolated right ventricular hypertrophy, the free wall of this chamber weighing 103 gm. as compared with 140 gm. for left ventricle and ventricular septum combined.

Lungs. On section the parenchyma was normal, but the pulmonary arteries were unusually prominent and atheromatous. No thrombi were seen.

The remaining viscera were not remarkable.

Microscopic findings

Lungs. Large elastic arteries showed moderate degrees of cystic medial necrosis and minor atheromatous lesions. In muscular arteries the development of external longitudinal muscle-bundles was more advanced than in Cases 1 or 2, and in many vessels they formed a complete layer (Plate 11, Fig. 10); this change was found in arteries as small as 300 μ. Medial defects were also present in muscular arteries, but less frequently than in Case 2. Organized occlusive thrombi were very common, particularly in the smaller muscular branches; in general the thrombosis affected segments less than 1 mm. in length. The lumina of some small arteries were completely obliterated by a dense fibrous tissue, sometimes traceable to a thrombus, but more often not. The walls of vessels containing either recanalized thrombi or fibrous plugs were characteristically pervaded here and there by capillaries of varying size, which could be shown to communicate with vascular channels in the obliterated lumen and with dilated capillaries in the adventitia. The extent of the mural vascularization varied considerably: in some cases a single capillary would cleave the wall, in others the lumen, media, and adventitia were occupied by numerous communicating capillary channels, producing a bizarre angiomatoid appearance, complicated sometimes by endothelial cell proliferation (Plate 11, Figs. 12 and 13). Rarely the capillary channels were traced to veins, but in most instances they terminated in the adventitia or in the alveolar capillaries. Occasionally the blocked vessels were associated with much larger thin-walled elastic vessels, closely resembling the structures recently described by Brewer (1955), and considered by him to arise above the obstruction and to provide, at least in some instances, an alternative pathway to the alveolar capillaries. In the present case they emptied into the alveolar capillaries, but their origin was not traced.

Although abnormally small muscular arteries were not readily encountered in casual sections, they were detected in serial sections and, as in Cases 1 and 2, they always terminated in congested but structurally normal arterioles. The lumina of many of these abnormally small arteries were severely constricted, or even obliterated, by dense fibrous tissue, but in some the intima was normal and the lumen completely patent (Plate 11, Fig. 11). The alveoli, alveolar capillaries, and pulmonary veins were in general within normal limits.

Other organs. No abnormality was found in the kidneys, pancreas, adrenals,

liver, spleen, intestine, uterus, brain, pituitary, mitral valve, left auricle, and left ventricle.

Comment. The course was short and progressive, with symptoms suggesting a low cardiac output. It is reasonable to ascribe the epileptiform attacks which occurred on effort to cerebral ischaemia, and it is possible, as in the patient of Howarth and Lowe (1953), that this sequence was due to acute right ventricular failure, for many attacks occurred after exertion had ceased. Certainly the patient died from this cause. The widespread occlusive lesions in the pulmonary vessels might be ascribed to repeated embolism. They could equally be interpreted as primary intrapulmonary thrombi, and this view is in harmony with the frequent finding of occlusive lesions in various forms of pulmonary hypertension, and seems preferable to a theory postulating repeated showers of small emboli, in this case all less than 1 mm. in size, from an unknown source. As in Case 2, the cause of the thrombi, if pulmonary, is unknown. Capillary invasion of occluded systemic arteries is well known (Winternitz, Thomas, and LeCompte, 1938; Akrawi and Wilson, 1950). In the present case the new vessels were localized to the segment closed by thrombus, and in most instances, as they did not communicate with the pulmonary artery proximal to the obstruction or with bronchial vessels, it seems unlikely that they provided an effective by-pass. We conclude that the hypertensive mechanism may be similar to that of Cases 1 and 2, namely a primary contraction of terminal arteries.

Case 4. I. E., a 37-year-old housewife, was admitted to the Royal Infirmary on 6.11.53. After the birth of her third child in April 1953 she became aware of shortness of breath on effort. This symptom progressed, but was never associated with substernal discomfort or syncope. During the same period she observed that her cheeks were becoming purplish in colour, and at the end of September noticed swelling of the ankles.

On examination she had a malar flush, and slight cyanosis of the nail-beds. There was a parasternal heave, moderate accentuation of the pulmonary second sound, a protodiastolic third sound, and a pulmonary systolic ejection click. The lowest blood-pressure was 130/90, but at other times readings of up to 155/120 were recorded. Other systems were entirely normal. Fluoroscopy showed great enlargement of the right ventricle and proximal dilatation of the pulmonary arterial tree. Electrocardiography showed extreme right ventricular hypertrophy. Red blood-cells were 5,500,000 per c.mm., and haemoglobin 108 per cent. Urea clearance was 94 per cent. of the average normal. Reactive hyperaemia was tested by the method of Lewis (1936), and the time was less than three seconds. The differential agglutination test was negative. Cardiac catheterization showed a mean pulmonary artery pressure in excess of 78 mm. Hg, an oxygen saturation of 65 per cent., and no shunt. Simultaneous brachial and femoral arterial oxygen saturations were 90 per cent., rising to 92 per cent. on effort. Vital capacity was 1,920 ml., and maximum ventilatory volume 81 litres per minute. She was treated with oral tolazoline, 25 mg. thrice daily, but without apparent benefit. When seen on 6.1.54 she was in congestive heart failure, and died from this cause in April 1954. Permission for an autopsy was not obtained.

Comment. This case remains incomplete. There is no evidence of acquired

cardiac disease, and the history is most unlike that of gross pulmonary hypertension complicating congenital heart disease. Neither is there evidence of parenchymal involvement of the lungs, as judged by the maximum ventilatory volume or the maintenance of the systemic arterial oxygen saturation on exertion. The natural history is very similar to that of Case 2, although there is less evidence of severe limitation of the cardiac output.

TABLE VII

The Effects of Exercise and Hexamethonium Bromide on Circulatory Dynamics in Case 5

State	Oxygen consumption (ml./min.)	Pulmonary arterial oxygen: vols. %	Pulmonary arterial oxygen: % saturation	Brachial arterial oxygen: vols. %	Brachial arterial oxygen: % saturation	Arteriovenous oxygen difference (vols. %)	Cardiac output (l./min.)	Pulmonary artery pressure: Systolic	Pulmonary artery pressure: Diastolic	Pulmonary artery pressure: Mean	Systemic blood-pressure: Systolic	Systemic blood-pressure: Diastolic	Systemic blood-pressure: Mean	Total pulmonary resistance (c.g.s. units)	Total systemic resistance (c.g.s. units)
Rest	211	14·4	73	18·7	94	4·3	4·9	59	24	37	98	49	66	525	1,019
Effort	450	13·6	69	19·0	95	5·4	8·3	91	33	54	..	..	84	500	781
Rest+C_6	262	13·9	70	18·4	93	4·5	5·8	58	25	38	102	58	71	460	912
Effort+C_6	537	12·2	62	18·1	90	5·9	9·1	114	43	67	120	76	84	545	693

C_6 = hexamethonium bromide, 12·5 mg. intravenous.

Case 5. A. T., a 40-year-old married woman, was admitted to the Royal Infirmary on 12.10.55. At the age of 13 she had a typical attack of acute rheumatic fever, but made a complete recovery, and was accepted for the nursing profession and successfully completed her training. She had two normal pregnancies at the ages of 27 and 33. In May 1955, on running fast after a bus, she became extremely distressed on account of breathlessness, intense exhaustion, and a heavy feeling in the chest; she was quite unable to speak for at least five minutes after stopping. Since then these symptoms had recurred many times, always on exertion; there was a curious inability to go another step, and she had to stop and rest until this passed away, which took about five minutes. The ease of induction varied; she observed that she was especially incapacitated in August when she had a sore throat, tending to improve again after this subsided. She had still been able to lead a fairly normal life, and had not appreciably deteriorated in the three months prior to her admission.

On examination her general condition was excellent, and there was no cyanosis. There was a faint parasternal heave, accentuation of the pulmonary second sound, a grade III pulmonary systolic murmur, and a variable presystolic third sound. Other systems were entirely normal. The blood-pressure was 120/80. On fluoroscopy there was no appreciable enlargement of the heart, but slight proximal dilatation of the pulmonary arterial tree. The electrocardiogram showed moderate right ventricular hypertrophy. Red blood-cells were 4,900,000 per c.mm., and haemoglobin 92 per cent. The urine was normal, serum-albumin 4·3 gm., and serum-globulin 3·3 gm. per 100 ml. The differential agglutination test was negative. No L.E. cells were found. Cardiac catheterization showed a moderate increase in pulmonary arterial pressure and hindrance, with no shunt. She was catheterized a second time, when observations were made on

the effect of exercise and of hexamethonium bromide (Table VII). Angiocardiography showed no abnormality of the heart or lungs. She is at present being treated with oral dibenzyline, 10 mg. thrice daily, but there has been no apparent improvement.

Comment. Although the limiting symptoms strongly suggest an inadequate cardiac output, this case is unusual in the variability of the symptoms and the absence of progression. The deterioration coinciding with a throat infection and subsequent improvement are also of great interest. Functional studies on effort, although demonstrating a consistently elevated total pulmonary hindrance, offer no support for the concept of a low cardiac output, the output response at oxygen-consumption levels of 300 to 350 ml. per sq. m. per minute being within the normal range (Table VII). There is an unusual variability in the pressure readings. In the first period of graded work the mean pulmonary artery pressure rose from 48 to 54 mm. Hg between the third and fourth minutes, a time by which a steady state has generally been obtained. At the end of the output period maximal effort was encouraged, but the pressure fell back to 46 mm.; the cardiac output was not measured at this time. On steady effort, after hexamethonium bromide had been given, the mean pressure rose to 67 mm. Hg. The symptoms of which she complained were never produced under experimental conditions. We suggest that in this case there is considerable lability of the pulmonary vascular hindrance, and that active vasoconstriction sometimes occurs to the point at which blood-flow through the lungs is seriously impeded. There is no evidence of arterial disease elsewhere, and hexamethonium had no demonstrable effect on dynamics.

Case 6. W. T., a 33-year-old male clerk, was admitted to the Royal Infirmary on 16.2.53. He had always enjoyed excellent health, and had served for six years in the Army in medical category 'A'. In October 1951 he became aware of shortness of breath on effort. This slowly worsened, and in mid-1952 became associated with a choking sensation and a feeling of intense fatigue, and he attended another hospital, where his symptoms were regarded as neurotic. A standard-lead electrocardiogram at this time was reported normal, but another three months later was reported as showing a striking change, in that grossly abnormal right axis deviation had appeared in the limb leads. On five occasions during the latter half of 1952 he lost consciousness during exercise.

On examination there was no cyanosis. There was a parasternal heave, slight accentuation of the pulmonary second sound, and a protodiastolic third heart sound, but no murmurs. The blood-pressure was 120/95. Other systems were entirely normal. Fluoroscopy showed great enlargement of the right ventricle and proximal dilatation of the pulmonary arterial tree. Electrocardiography showed right ventricular hypertrophy, but with upright T waves over the right precordium. Red blood-cells were 5,570,000 per c.mm., and haemoglobin 100 per cent. The differential agglutination test was positive. L.E. cells were not found. Cardiac catheterization showed a mean pulmonary artery pressure of 59 mm. Hg, with an oxygen saturation of 44 per cent., and no shunt. The systemic arterial oxygen saturation was 89 per cent., and did not alter on exercise. Studies of lung function showed a slight diminution in maximum ventilatory volume (77·4 litres per minute; predicted normal 123 litres per minute), but otherwise gave normal results. He was given oral tolazoline, 25 mg. thrice daily,

but progressively deteriorated. In June 1953 he developed congestive heart failure, and died from this cause on 1.11.53.

Post-mortem macroscopic findings

There was gross subcutaneous oedema of the lower limbs and trunk, and the abdomen and thorax contained large quantities of clear straw-coloured fluid, the serous surfaces being normal. The heart (405 gm.) was normal apart from a dilated right auricle and a hypertrophied and dilated right ventricle, the free wall of this chamber weighing 90 gm. compared with 157 gm. for the left ventricle and ventricular septum combined. The pulmonary artery trunk was thickened and dilated, but its intimal surface was smooth; otherwise the great vessels were normal. The bronchial arteries at the hilum of the lungs appeared normal.

The *lungs* presented no definite abnormality apart from prominent pulmonary arteries protruding above the cut surface. There were no signs of thrombosis or emboli.

Other viscera. The liver (1,560 gm.) showed a mild cirrhosis, and a normal extrahepatic biliary tract. All other organs were either passively congested or normal.

Microscopic findings

Lungs. Elastic arteries showed moderately severe atheroma only. The medial coat of muscular arteries was not so thick, and the formation of external longitudinal bundles not so prominent, as in Cases 1, 2, and 3. In contrast with the preceding cases there was arteritis, mainly involving muscular arteries, and arteriolitis. In the larger vessels the lesion was often indistinguishable from either recent or old polyarteritis nodosa, though milder forms of arteritis, not so easily classified, were also seen (Plate 12, Figs. 14, 15, and 16). Severe lesions were usually associated with some fibrous intimal sclerosis, but not with thrombosis. In the smaller branches, in which milder lesions were commonest, the fibrous intimal thickening was often concentric, and caused severe constriction of the lumen (Plate 12, Fig. 16*a*). Occasionally alveoli near the severe lesions in the larger branches were filled with a fibrinous haemorrhagic exudate, presumably due to a local extension of the perivascular inflammation, for alveolitis was not encountered elsewhere. Arteriolitis was usually seen as a perivascular and intimal oedema scantily infiltrated with inflammatory cells; sometimes the intima was swollen and degenerate, but arteriolonecrosis or hyaline arteriolosclerosis typical of that occurring in systemic hypertension was never observed. (Plate 12, Fig. 17). Very occasionally the lumen of these small vessels was greatly reduced by swollen hyperchromatic cells arranged concentrically, the appearances closely resembling the 'pulmonary hyperplastic arteriolosclerosis' described by Parker and Weiss (1936) in cases of mitral stenosis.

The lumina of some muscular arteries were obstructed or occluded over a short distance by fibrous formations with the appearance of organized thrombi. This sometimes occurred (as in Cases 2 and 3) in the absence of vasculitis, recent or old, but in many arteries there were signs of an old destructive lesion of the vessel wall. The occluded vessel was often permeated by vascular channels communicating with adventitial capillaries through transmural branches—a process essentially the same as that encountered in obliterated arteries in Case 3. The external diameters of the terminal muscular arteries were generally within normal limits, and the structural sequence characterizing the termination of the pulmonary artery tree in Cases 1, 2, and 3 was not a conspicuous feature of this case. The alveolar capillaries and the pulmonary veins were normal.

Other viscera. There was an early centrilobular cirrhosis of the liver, and

passive congestion of the spleen and kidneys. But no significant abnormality was found in the heart, pancreas, pituitary, adrenals, or small intestine.

Comment. The natural history is similar in many ways to that of Case 2, with a short history of symptoms largely ascribable to a low cardiac output, and an absence of symptoms suggestive of congestion of the pulmonary capillary bed. The abnormal physical findings were confined to those of pulmonary hypertension. The electrocardiographic reports indicate the appearance of right ventricular hypertrophy between the eighth and 11th months after the onset of symptoms. Although this observation is based on standard leads only, it strongly suggests that pulmonary hypertension did not antedate the onset of symptoms by an appreciable interval. The histological findings are quite distinct from those described in Cases 1, 2, and 3, apart from a hypertrophy of the medium-sized muscular arteries. Pulmonary arteritis and arteriolitis may have been the primary abnormality in this case, for there was no sign of these lesions in the preceding cases, and they were clearly not a terminal episode. It is questionable, however, whether the organic obstruction resulting from arteritis, arteriolitis, and organized thrombi was sufficiently severe and widespread to account alone for the hypertension. There was no definite evidence of widespread vasoconstriction of the terminal arteries; and the possibility of a superadded vasoconstriction in larger arteries, where arteritis was most common, is difficult to assess morphologically.

Case 7. B. H., a 28-year-old married woman, was admitted to the Royal Infirmary on 31.12.54. At the age of 21 she had an uneventful pregnancy, but shortly after the birth of the child she began to experience Raynaud's phenomenon precipitated by cold. Apart from this her health remained good until two years before admission, when she first noticed dyspnoea on effort. The dyspnoea progressively worsened, and became associated with a feeling of intense fatigue. In July 1954 she attended the out-patient department of another hospital; no abnormality was found, and she was reassured. The systemic blood-pressure was noted to be 130/80, and a standard-lead electrocardiogram showed borderline right axis deviation. In September she developed swelling of the ankles, and also frontal headaches of increasing severity.

On examination she was obviously very ill. There was a left facial palsy which had been present since birth. The fingers were cold and cyanotic, but there was no general cyanosis. There was a parasternal heave, a grade I pulmonary systolic murmur, accentuation of the pulmonary second sound, and a presystolic third sound. The neck veins were engorged, there was gross oedema, and the liver extended to three finger-breadths below the costal margin. There were retinal haemorrhages, but no papilloedema, the left triceps jerk was absent, and the plantar response extensor. The blood-pressure was 160/145. Fluoroscopy showed enlargement of the heart, mainly of the right ventricle, and proximal dilatation of the pulmonary arterial tree; there was an opacity of uncertain nature in the left lower zone. Electrocardiography showed extreme right ventricular hypertrophy. Red blood-cells were 4,800,000 per c.mm., haemoglobin 92 per cent., and white blood-cells 18,200 per c.mm., 86 per cent. being polymorphs. Serum-albumin was 2·2 gm., and serum-globulin 4·3 gm. per 100 ml. with an increase in the α_1, α_2, γ_1, and γ_2 fractions. The differential agglutination test was negative, and L.E. cells could not be found. The blood-urea was 58 mg. per 100 ml. Routine treatment for heart failure was begun. On

1.1.55 the patient developed retention of urine, and thereafter frequent catheterization was required. On 3.1.55 right ilio-femoral thrombosis occurred, and anticoagulants were commenced. On 10.1.55 signs of a urinary infection appeared, and this was controlled with antibiotics. On 22.1.55 cortisone was commenced with 300 mg. per day, falling to 100 mg. per day in seven days. There was no improvement, and she died suddenly on 31.1.55.

Post-mortem macroscopic findings

The whole of the right leg was oedematous, probably from extensive thrombosis of the right internal iliac vein. The distal halves of all the fingers were livid, but neither ulcerated nor scarred; the digital skin was thin but mobile. There was an isolated right ventricular hypertrophy, the free wall of this chamber weighing 104 gm. compared with 127 gm. for the left ventricle and septum combined. An atrial septal defect ($2 \times 1{\cdot}5$ cm.) was present. The coronary arteries were patent, but probably thicker than normal. The pericardial sac contained an excess of clear amber fluid.

Lungs. The mid-zone of the right lung was adherent posteriorly, and both pleural cavities contained a small quantity of clear fluid. Apart from a few small recent haemorrhagic infarcts and prominent pulmonary arteries, both lungs appeared healthy.

Other viscera. Both renal pelves were dilated, inflamed, and flecked with pus, and the renal cortical pattern was obscured by barely visible yellowish foci, which were also scattered about the medulla. There was a mild cystitis. The spleen contained a pale infarct, but no thrombi were detected in the splenic vessels.

Microscopic findings

Lungs. Pathological changes were confined to the pulmonary arteries, apart from rare microscopic areas of alveolar fibrosis not associated with dust and interpreted as healed foci of interstitial pneumonitis. Elastic arteries were atheromatous. External longitudinal muscle had developed in some large muscular arteries, which otherwise were normal. In contrast, the lumina of most muscular arteries 250 to 80 μ in diameter were reduced by a concentric intimal fibrosis or fibroelastosis, characteristically unaccompanied by inflammatory infiltration or degeneration of media or adventitia. This lesion was often localized to a short segment of the vessel, and gradually gave way to a subintimal oedema or serous coagulum (Plate 13, Figs. 18, 19, and 21). Very occasionally this intimal oedema contained scanty inflammatory cells, and more rarely these infiltrated the media and adventitia (Plate 13, Fig. 20); but a fibrinoid arteritis was never encountered in numerous serial sections. Recent thrombi were rare, and old recanalized thrombi were not seen. Abnormally small muscular pulmonary arteries, similar to those found in Cases 1, 2, and 3, were not infrequently encountered.

Heart. Microscopic areas of myocardial fibrosis occurred infrequently in the posterior wall of the left ventricle. The left coronary artery showed a uniform concentric intimal fibroelastosis, without the fatty deposits usually associated with atherosclerosis.

Kidneys. There was a subacute pyelonephritis, evidently of recent origin, since there was little or no interstitial or periglomerular fibrosis. Concentric intimal fibrosis was present in interlobular arteries, in the vicinity of focal inflammatory lesions and in areas not so involved. Hyaline arteriolosclerosis or arteriolonecrosis was not seen. In the renal pelvis fibrinoid arteritis resembling polyarteritis nodosa was found.

Adrenals. The parenchyma was normal, but recent fibrinoid arteritis was present in the capsular tissues (Plate 13, Fig. 22).

Liver. There was a mild arteritis of the larger hepatic vessels, characterized by a pleomorphic cellular infiltration of the intima, media, and adventitia, without fibrinoid formation. The parenchyma was congested, but not otherwise abnormal.

Pancreas. Most of the arteries showed a severe concentric intimal fibrosis or fibroelastosis, without inflammatory cellular infiltration or mural degeneration (Plate 13, Fig. 23*b*).

The *palmar digital arteries*, and small arteries in the volar tissues in the distal part of the forearm, showed a severe concentric intimal fibroelastosis similar to that seen in the pancreatic, renal, coronary, and pulmonary arteries (Plate 13, Fig. 23*a*).

The *spleen* was normal apart from the infarct already mentioned. The *internal iliac artery* was normal, but the accompanying vein contained a partly organized thrombus, and there was inflammatory cellular infiltration in the wall and perivascular tissues. The *oesophagus* was within normal limits.

Comment. This patient presented clinical evidence of diffuse arteritis, Raynaud's phenomenon antedating other cardiovascular symptoms. There is no evidence as to the duration of the pulmonary hypertension; the limb-lead electrocardiogram taken in July 1954 is identical in appearance with that taken on admission in December and, although not interpreted as being abnormal at that time, is consonant with the presence of right ventricular hypertrophy. At that time the systemic pressure was normal, and the short duration of the systemic hypertension is borne out by the normal weight of the left ventricle and septum, and the absence of arteriolosclerosis. Pathological studies confirm the widespread nature of the disease, the oldest and predominant lesion in limbs and viscera being a concentric intimal fibrosis or fibroelastosis not associated with inflammatory infiltration or mural degeneration. It may reasonably be assumed, therefore, that the pulmonary arterial lesions of this type are a manifestation of this generalized arterial disease. While the involvement of the pulmonary arterial tree offers a satisfactory explanation for the pulmonary hypertension, it is difficult to classify this case. The predominant arterial lesion closely resembled that found in progressive systemic sclerosis (scleroderma) (personal observation), while others were like polyarteritis nodosa. There were many features which were not characteristic of either disorder; these points are discussed in more detail on pages 111 and 112. The cystitis, pyelonephritis, and pelvic venous thrombosis appear to have been coincidental events occurring shortly before death. It is probable that the atrial septal defect is also an incidental finding.

Case 8. E. H., a 27-year-old nulliparous housewife, was admitted to the Royal Infirmary on 21.1.53. In 1945 she developed an arthritis of rheumatoid type, which was treated by intramuscular injections of a gold salt. She improved, but in 1946 experienced Raynaud's phenomenon of the fingers. In 1949 she began to have dyspnoea on exertion. This progressed, and towards the end of 1950 she noticed swelling of the ankles. She was admitted to hospital at that time, and was found to be in congestive heart failure, the aetiology not being determined. She responded to treatment, but swelling of the feet recurred periodically during the next two years.

On examination she was slightly cyanotic, there was a parasternal heave, a grade II pulmonary systolic murmur, moderate accentuation of the pulmonary second sound, and signs of congestive heart failure. The fingers were cold, with sclerodactylous changes, and small necrotic areas on the tips. The only joint abnormality was painless limitation of movement of the fingers and wrists. The blood-pressure was 110/80. Fluoroscopy showed moderate enlargement of the right ventricle and proximal dilatation of the pulmonary arterial tree. Electrocardiography showed extreme right ventricular hypertrophy. Red blood-cells were 4,800,000 per c.mm., and haemoglobin 90 per cent. The differential agglutination test was positive. Cardiac catheterization showed a mean pulmonary artery pressure of 48 mm. Hg, with an oxygen saturation of 41 per cent., and failed to demonstrate any shunt. The systemic arterial oxygen saturation was 87 per cent. L.E. cells were not found. The patient improved on routine treatment for congestive heart failure, although signs of an elevated venous pressure persisted. In March 1953 she was given a 10-day course of cortisone, with no apparent effect on her condition, and when last seen in June 1954 she was still in heart failure, which required the regular administration of digitalis and mercurial diuretics.

Comment. This case is linked to Case 7 by the presence of occlusive digital arterial lesions. In Case 7 the hypertension was considered to be due to pulmonary arterial lesions similar to that occurring in the fingers. In the absence of an alternative explanation, it is reasonable to ascribe the hypertension to a similar cause in the present case. The relatively low pulmonary pressure may have been due to the heart failure present at the time of catheterization, and the chronicity of the failure suggests that the heart itself may have been primarily affected.

Case 9. W. L., a 37-year-old police sergeant, was admitted to the Royal Infirmary on 28.10.52. As long as he could remember he had been 'on the short-winded side'. He could and did lead a normal life, but never took part in active sports. In 1936 he coughed up a small quantity of blood, and this recurred on five occasions between 1936 and 1951. Over Christmas and the New Year 1951/2 he suffered several larger haemoptyses of up to half a cupful of blood, but had no further bleeding up to the time of his admission. He had also experienced occasional syncopal attacks, associated with nausea but not actual loss of consciousness, and unrelated to effort. His wife said he had always looked 'like a publican' and had a high colour.

On examination he had a purplish complexion, the cardiac impulse could not be felt, the pulmonary second sound was accentuated, and there was a proto-diastolic third heart sound, but no murmurs. The blood-pressure was 120/70. Other systems were within normal limits. Fluoroscopy showed considerable enlargement of the heart, mainly the right ventricle, and proximal dilatation of the pulmonary arterial tree. Electrocardiography showed extreme right ventricular hypertrophy. Red blood-cells were 7,920,000 per c.mm., and haemoglobin 140 per cent. The differential agglutination test was positive. On cardiac catheterization the mean pulmonary artery pressure was found to be in excess of 78 mm. Hg, but the investigation had then to be abandoned on account of peripheral circulatory failure, with nodal bradycardia at a rate of 30 per minute. The attack was subjectively similar to those which had occurred spontaneously. He remained well until August 1953, when he was readmitted on account of acute frontal sinusitis. While under treatment he developed right-

sided pleural pain and friction, followed by haemoptysis. Six days later he had a massive haemoptysis, and expired immediately.

Post-mortem macroscopic findings (Dr. H. de C. Baker)

The body was that of a heavily built man, with slight oedema of the ankles. The heart (700 gm.) was enlarged, and there was obvious hypertrophy of the right ventricle. The combined weight of the left ventricle and septum (235 gm.) was above the upper limit of normality, but the free wall of the right ventricle (182 gm.) indicated a relatively greater increase in muscle in this chamber. The heart was otherwise normal.

Lungs. Both were somewhat bulky, the left weighing 790 gm., the right 1,100 gm. On section neither emphysema nor fibrosis could be found, but there were recent haemorrhagic infarcts in the right lower and middle zones. Thrombi were detected only infrequently in the small pulmonary arteries. The larger pulmonary arteries were dilated, but not noticeably thickened.

Other viscera. Apart from passive congestion the remaining viscera were not remarkable.

Microscopic findings

Lungs. Atheroma of the elastic arteries was less advanced than in the preceding cases, and most of these vessels had a normal intimal surface. Some of the small lateral branches of the elastic arteries were completely occluded at their origin, and for a short distance beyond, by dense fibroelastic tissue. Very rarely a large muscular artery presented an appearance similar to the healed phase of polyarteritis nodosa; but most of the larger muscular arteries appeared normal, though probably greatly dilated as judged by the relative size of neighbouring bronchi. In contrast to all the preceding cases, large anastomotic channels (up to 200 μ) were found connecting bronchial arteries (lying in the walls of small cartilaginous bronchi) with muscular pulmonary arteries about 250 μ in diameter. In some instances, at least, the walls of these anastomotic vessels consisted of a normal intima supported by thick elastic lamellae containing only traces of muscle. The vessel was characteristically tortuous, and followed a course typical of the bronchopulmonary anastomotic arteries described by Verloop (1948) and Tobin (1952). In two blocks it was possible to prove the anastomosis in serial sections; but there were indications in sections from various parts of the lungs that these bronchopulmonary channels were far from being rare. In the example illustrated in Fig. 24 (Plate 14) it will be seen that the pulmonary branch involved in the anastomosis is blocked proximally, and dilated distal to the point at which the anastomosis occurs. It is not known whether this finding characterized all anastomotic sites. Sections of the hilar regions contained unusually large and numerous bronchial arteries, and large thin-walled varicose vessels occupied the walls of some bronchi which were otherwise normal (Plate 14, Fig. 25); such bronchial vascular structures were not seen in the preceding cases.

Many of the pulmonary artery branches distal to the anastomoses appeared to be dilated, but otherwise normal. Other branches of the same arterial trunk sometimes contained longitudinal muscle in the intima, which extended into the smallest arterial or more rarely into the arteriolar subdivisions, greatly narrowing the lumina of these vessels. Invariably, however, this intimal thickening tapered out before the terminal arteriolar segments were reached.

Comment. This case presents many unusual features. The history is long; indeed, slight incapacity seems to have been present almost throughout life, but it did not progress. Haemoptysis was a prominent symptom, ultimately

causing death, and there was an unusual polycythaemia. Only one other patient complained of haemoptysis (Case 10). The histological findings were unique in that there were large pre-capillary bronchopulmonary anastomoses, some with poorly developed muscle layers and a wide lumen of up to 200 μ in diameter. There was also left ventricular hypertrophy, a finding in strict contrast to the other cases. The structure of many of the terminal pulmonary arteries was also unusual, differing from other cases of unexplained pulmonary hypertension in that the main abnormality was the development of an internal longitudinal muscle coat resembling the structure of *Sperrarterien* (compare page 88). It is possible that the flow through these anastomotic channels was considerable, and there is some evidence for this in the left ventricular hypertrophy. The dilated thin-walled vessels in the submucosa of some bronchi, presumably the source of the haemoptysis, are also evidence of an increased bronchial circulation. The long history, cyanosis, and polycythaemia suggest that intermittent reversal of the shunt had been present for some time.

Case 10. G. B., a 23-year-old male clerk, was admitted to the Royal Infirmary on 18.2.52. He had always enjoyed good health, playing games at school and being accepted in category 'A' for H.M. Forces in 1945; he was not called up on account of his occupation. Early in 1949 he developed an aching pain in the left chest, which occurred on effort but persisted for as long as an hour after cessation. During 1950 this symptom spontaneously cleared, and was replaced by increasing breathlessness on effort, until by January 1952 he could walk only 150 yards on level ground. There was no orthopnoea, but during 1951 he brought up a little blood-streaked sputum on several occasions. In December 1951 he noticed swelling of his legs. He was admitted to a hospital in February 1951, and the following observations were made: cyanosis, but no clubbing; a parasternal heave and pulsation in the second left space; a harsh systolic murmur loudest to the left of the sternum; pulmonary second sound accentuated; blood-pressure 170/135. Other systems were normal. A few days later the blood-pressure was noted to be 140/115.

On examination in January 1952 there was slight cyanosis of the lips and clubbing of the fingers, a left parasternal heave, a grade III pulmonary systolic murmur, and an accentuated and split pulmonary second sound; the blood-pressure was 125/100. Apart from engorgement of the neck veins and a palpable liver, other systems were normal. An X-ray of the chest showed moderate enlargement of the right ventricle, proximal dilatation of the pulmonary arterial tree, and normal peripheral lung fields. Angiocardiography failed to demonstrate a shunt. Electrocardiography (February 1951) showed incomplete right bundle-branch block, the duration of QRS being 0·11 second, and probable right ventricular enlargement; it was not repeated in 1952. Red blood-cells were 5,910,000 per c.mm., white cells 7,000 per c.mm., with a normal differential count, and haemoglobin 110 per cent. He was considered to be suffering from congenital pulmonary stenosis, and was submitted to operation. No stenosis was found, and he died six hours later.

Post-mortem macroscopic findings (Dr. J. C. Burne)

The body was that of a well-built man, with cyanotic extremities. The heart weighed 680 gm., and showed isolated right ventricular hypertrophy. The lungs were congested, and the larger branches of the pulmonary artery were atheromatous. Other organs showed only passive congestion.

Microscopic findings

Lungs. Several blocks were available for section, and in all of them the pulmonary arteries showed no structural abnormality; they were thin-walled, and possibly dilated as judged by the relative size of adjacent bronchi. The alveoli and veins were also normal. A dilated, thin-walled bronchopulmonary anastomotic vessel, 150 to 250 μ in diameter, was proved in one block, and evidence of similar anastomoses was seen in others (Plate 15, Figs. 26 and 27). The walls of cartilaginous bronchi in the vicinity of the anastomoses contained dilated blood-vessels, but no inflammatory infiltration.

Other viscera. No significant abnormality was found in the heart, kidneys, adrenals, or oesophagus. There was early hepatic cirrhosis.

Comment. Before the onset of failure the main symptom was purely dyspnoea on effort, with occasional haemoptysis. The nature of the initial chest pain is uncertain, but it is not reminiscent of angina. Although the pulmonary arterial pressure was not measured, the clinical, radiological, electrocardiographic, and pathological findings together provide incontrovertible evidence of pulmonary hypertension. On histological examination wide bronchopulmonary anastomoses were found, but their frequency and distribution were unknown. Apart from these anastomotic channels the pulmonary arteries appeared normal or, at most, dilated, the occasional arterial blocking and intimal muscular thickening seen in Case 9 being absent. Cases 9 and 10 are similar in showing bronchopulmonary anastomoses, and it is significant that these two patients were the most cyanotic, the only ones with haemoptysis, and had unusually large hearts.

Discussion

Unexplained pulmonary hypertension is relatively infrequent. It is difficult to gauge the incidence, for cases have been reported under so many different diagnoses; Wood (1950) found six cases of what he described as 'idiopathic pulmonary hypertension' among 200 patients with suspected congenital heart disease subjected to cardiac catheterization. At least 30 well-documented cases of pulmonary hypertension not secondary to any recognized cardiac or pulmonary disease have been reported since 1940. Some two-thirds of the patients were women, and this accords with the sex incidence in our series of eight women and two men. With the exception of nine children under the age of three years reported by Berthrong and Cochran (1955), the majority have been young adults.

Symptoms and signs. Dyspnoea, an invariable symptom in our patients and in the recorded cases, differs from that usually present in cardiac or pulmonary disease. It was confined to exertion and in seven cases associated with fatigue, substernal oppression, faintness, or syncope. Orthopnoea was never observed, and in the later stages the contrast between the distress on effort and the well-being at rest was very striking. The normal results of spirometry, where it was done, accord with the findings of Werkö and Eliasch (1952), and suggest that alterations in pulmonary distensibility or viscous resistance are not concerned. The symptom-complex in some cases suggests a limited cardiac output, and in

six patients there was support for this concept in the large resting arteriovenous oxygen difference. Moreover, the increase in output on effort in Case 1 was small (Table V), and this was so in Werkö and Eliasch's patient. Substernal pain on effort, present in three cases, has long been known to occur in pulmonary hypertensive states: Posselt (1908), in cases of mitral stenosis with pulmonary arteriosclerosis, described attacks of 'dysphagia intermittens angiosclerotica pulmonalis'. Viar and Harrison (1952) suggested that it might be caused by distension of the pulmonary artery, but we agree with Wood (1954) who, discussing angina in mitral stenosis, concluded it was due to functional coronary insufficiency consequent upon a low cardiac output. Effort syncope occurred in three of our patients, and in five of 30 reported cases. In its simpler form it may follow transient cerebral anaemia due to a low cardiac output. In Case 3 the attacks developed two or three minutes after effort had ceased, were of long duration, and were associated with peripheral circulatory failure; death ultimately occurred in such an attack. Howarth and Lowe (1953) have shown that this type of attack is due to acute right ventricular failure consequent upon the rise in pulmonary arterial pressure. Haemoptysis is rare in reported cases, and was a prominent symptom in only two of our patients (Cases 9 and 10). It was apparently due to haemorrhage from dilated vessels in the submucous layer of the bronchi. This point will be discussed again in relation to the site and nature of the lesion. Apart from these two cases, cough was never a symptom.

The physical findings in the cardiovascular system are those indicating pulmonary hypertension, namely a diffuse cardiac impulse, a triple rhythm, and one or more of the following: accentuation of the pulmonary second sound, a pulmonary systolic murmur, or a Graham Steell murmur (Bedford, 1951). It is of interest that, despite the high pressures, a Graham Steell murmur was never heard in our patients. About one half of the reported cases have shown cyanosis, but whereas some have reported it as terminal and peripheral (East, 1940; Howarth, McMichael, and Sharpey-Schafer, 1947; Dresdale, Schultz, and Michtom, 1951), others have thought it of central origin (Ulrich, 1932–3; de Navasquez, Forbes, and Holling, 1940; Brill and Krygier, 1941). Three of our patients were cyanotic (Cases 10, 9, and 4) and the remainder, with the exception of Case 5, had a malar flush not dissimilar to the facies of severe mitral disease. Slight arterial oxygen unsaturation was found in six of the eight cases in which it was estimated, but saturation was never below 87 per cent. With the exception of one of the patients of Parmley and Jones (1952) in whom the red cell count was over 7,000,000 per c.mm. and the arterial oxygen saturation was 77 per cent., cyanosis, when present, has generally been reported as slight. Parmley and Jones's patient also complained of a chronic cough with purulent sputum, but no post-mortem examination was made, so no comparison can be drawn. Few estimations of arterial oxygen saturation have been reported, but Blount and McCord (1954) found slight unsaturation in five of nine cases. The slight unsaturation generally found in our patients (Table II) indicates an increase in venous admixture, but only in Cases 9 and 10 were bronchopulmonary communications demonstrated through which this mixing could take place. There

is no evidence that the unsaturation in the other cases was due to a diffusion defect, for none of the five major criteria listed by Baldwin, Cournand, and Richards (1949), on which a diffusion defect may be diagnosed, was satisfied. Presumably, although we were unable to demonstrate them, pulmonary arteriovenous shunts must have existed in these lungs. The very slight polycythaemia generally found may be reasonably ascribed to tissue ischaemia. Only in Case 9 was there severe polycythaemia, and here the conditions for a right-to-left shunt were present and may sometimes have resulted in a considerable fall in systemic arterial saturation.

Radiology and electrocardiography. The radiological findings are characteristic of pulmonary arterial hypertension with a normal capillary bed, and may be summarized as follows: enlargement of the right ventricle, dilatation of the proximal portion of the pulmonary arterial tree, with narrowing of the distal branches, and normal peripheral lung fields (Plate 16, Figs. 28*a*, *b*). These findings were common to all our cases. The close relation between these signs and the degree of pulmonary hypertension was pointed out by Wade, Werkö, Eliasch, Gidlund, and Lagerlöf (1952) and confirmed in arteriographic studies by Davies, Goodwin, Steiner, and Van Leuven (1953). 'Hilar dance', an indication of increased flow (Campbell, 1951), was not seen on fluoroscopy. The electrocardiograph invariably showed evidence of right ventricular enlargement, usually extreme, but it is probable that in Case 6 symptoms antedated the electrocardiographic changes. A 'right ventricular' electrocardiogram is the rule in the reported cases.

Causal mechanisms. It is clear that our group is not homogeneous, for there are significant differences in the natural histories and in the pathological findings. In the ensuing discussion the cases will be considered in the order in which they have been reported.

Five patients (Cases 1, 2, 3, 4, and 6) presented a fairly uniform picture of progressive symptoms ascribable to a low cardiac output, with death from right ventricular failure in from 10 to 30 months. In all five the physical findings were confined to those of pulmonary hypertension. This short, almost 'malignant', course is typical of many of the described cases of 'primary' pulmonary hypertension. The most illuminating case, on account of the clarity of the histological picture in the lungs, is Case 1. The lungs of this 11-year-old girl, who had enjoyed perfect health until 15 months before her death, showed only one major abnormality, unusually small muscular arteries with an external diameter of 80 to 40 μ. Pulmonary artery thromboses and intimal fibroelastosis were absent. These abnormally small muscular arteries, which also occurred in Cases 2, 3, and 6, joined apparently normal arterioles which, structurally, would seem to be incapable of actively hindering blood-flow. The abnormally small muscular vessel is not a specific lesion, for it is also found in cases of congenital or acquired heart disease characterized by severe pulmonary hypertension, but not in control sections from normotensive cases (Table IV). It may be explained in three ways: (1) the persistence of a foetal type of pulmonary vasculature (Goodale and Thomas, 1954); (2) new growth of muscle in what are normally non-muscular

arterioles; (3) active contraction of normal arteries. We have no clear knowledge as to how long the high pressure had been present prior to the onset of symptoms and, although most of our patients had undergone routine medical examinations at different times and been pronounced healthy, it must be admitted that the signs of pulmonary hypertension could easily be missed if their presence was not anticipated. The excellent health invariably enjoyed before the onset of symptoms is very strongly against congenital hypertension, for patients with a high pulmonary resistance are usually disabled, a disability which has been ascribed to loss of the normal flexibility of the pulmonary circuit (Deuchar and Knebel, 1952). Moreover, although abnormally small muscular arteries are found in foetal lungs (Table IV), their elastic membranes are poorly developed by comparison with those found in our patients (Plate 8, Fig. 2). We consider it unlikely, therefore, that there is a persistence of foetal structure. Heath and Whitaker (1955*b*) have postulated new growth of muscle in non-muscular arterioles to account for the abnormally small muscular arteries found in cases of mitral stenosis and patent ductus arteriosus with pulmonary hypertension. Such a structural adaptation to a change in function must imply that the obstruction to flow is distal to these vessels. In our cases the arterioles which these small arteries joined were non-muscular, and appeared morphologically normal and apparently incapable of active contraction; for this reason we consider this thesis to be untenable. In commenting upon Case 1, we noted that the mean cross-sectional area of the circular media in arteries with a mean external diameter of 50 μ was virtually the same as in those of 99 μ in the control subjects. A contracted, but otherwise normal, terminal artery would therefore have the appearance of these abnormally small muscular arteries, and the wrinkled elastic membranes conform with this interpretation. If this hypothesis is correct, the hypertension occurs on account of an increased hindrance proximal to the artery-arteriolar junction, and this in turn is due to active contraction of the small arteries. Strong indirect evidence that this is the site of the obstruction to flow is afforded by the absence of signs of an alveolar-capillary diffusion defect and the normal spirometry; and Werkö and Eliasch (1952) also found in their patient that the increased resistance lay proximal to the capillary bed.

In addition to abnormally small muscular arteries, the more proximal arteries in Cases 2 and 3 were obstructed by lesions of two main types, namely pulmonary artery thrombi and intimal fibroelastosis. Both these lesions have been reported many times in cases of unexplained pulmonary hypertension, and have been regarded by some workers as the primary cause of the high pressure. Some pathologists have regarded the thrombi as embolic (Means and Mallory, 1931–2; Goedel, 1930; McKeown, 1952). Owen, Thomas, Castleman, and Bland (1953), reviewing 8,000 autopsies, found 12 cases of unrecognized pulmonary embolism, many with right ventricular hypertrophy. They suggested that many cases of 'primary' pulmonary hypertension may be explained in this way. We do not consider that chronic embolization caused the hypertension in Cases 2 and 3, and prefer to regard the thrombosis as autochthonous. In Case 2 the thromboses, in large and small vessels, were all of too recent origin to be responsible

for the syndrome. In Case 3 both recent and old thrombi were found, but only in small vessels; if embolic, there must have been showers of small particles all less than 1 mm. in size. In neither case was there an obvious source of emboli. If the thrombi in Case 3 were the primary lesion, it is difficult to account for the abnormally small arteries distal to them; this argument also applies to fibroelastosis (see below). There is also no convincing experimental evidence that repeated intravenous injection of fibrin or blood-clot will cause chronic pulmonary hypertension, though some degree of arteriosclerosis invariably occurs (Harrison, 1948, 1951; Barnard, 1954). Fibroelastosis is normally found with increasing frequency in older age-groups, most commonly at branching sites, and, if analogy may be drawn with systemic arteriosclerosis, it will be more pronounced if there is hypertension. This lesion has been reported in various types of pulmonary hypertension, but the degree of obstruction produced by it is very variable (Ulrich, 1932–3, Cases 1 and 2; Brenner, 1935; Brown, Heath, and Whitaker, 1955; Heath, Brown, and Whitaker, 1956). It also occurs in pulmonary stenosis, in which the pulmonary arterial pressure is certainly not raised (O'Neal and Thomas, 1955). The ubiquity and variability of this type of pulmonary arterial lesion renders it improbable that it is the primary cause of the obstruction to flow, and moreover we know from Case 1 that such lesions may be absent.

Only one of our patients (Case 5) had a history of rheumatic fever, and she was also unique in the mildness and variability of her symptoms. One other case of pulmonary hypertension occurring in a patient who had had rheumatic fever (two years previously) has been reported (Aitchison and Richmond, 1955), and arteritic lesions were found in the lungs. The authors concluded that the arteritic lesions were too recent to be ascribable to a rheumatic arteritis occurring two years before death. In the absence of pathological studies no conclusions can be drawn as to the relationship of the rheumatic fever to pulmonary hypertension in our patient.

In Case 6, that of a man presenting a clinical syndrome very similar to that of Cases 1, 2, 3, and 4, there were throughout the lungs arteritic lesions characteristic of polyarteritis nodosa. It is impossible to gauge the frequency of such lesions in reported cases of 'primary' pulmonary hypertension, but in at least some such cases they have been described (Braunstein, 1955; Berthrong and Cochran, 1955; Elwood, 1955). McKeown (1952), in a post-mortem survey, found eight cases of an apparently similar clinical syndrome, four with polyarteritis nodosa, and four with no arteritic lesions. Pulmonary involvement in polyarteritis nodosa is common, but pulmonary hypertension is unusual (Rose, 1956). With the exception of a few cases of mitral stenosis (Symmers, 1952; Braunstein, 1955) and one case of Eisenmenger's complex (Old and Russell, 1950), arteritis typical of polyarteritis nodosa has not been described in secondary pulmonary hypertension. In our patient either the arteritis can be regarded as primary and the cause of the high pressure, and this is the mechanism we have inferred in the two cases of generalized arteritis (Cases 7 and 8), or the hypertension has incidentally disclosed a generalized susceptibility to this type of

arterial lesion. If this is so, and the arteritis incidental, the case may be grouped with Cases 1, 2, 3, 4, and probably 5. It is not possible to be sure which sequence of events is correct; clinically the cases appear to be indistinguishable.

We have very little evidence as to the cause of the vasocontraction which we have inferred to be the basic mechanism of the increased resistance in Cases 1, 2, 3, 4, 5, and possibly 6. The age and sex incidence in these patients does not suggest that pulmonary hypertension is a graded characteristic such as Pickering (1955) argues in the case of systemic hypertension. There are no normal homoeostatic mechanisms known of which the disease might be an exaggeration or misuse. The family history was not contributory in any of our cases, and we are aware of only one published case in which there may have been a hereditary factor (Dresdale, Michtom, and Schultz, 1954). Dresdale, Schultz, and Michtom (1951) claimed that the injection of 2-benzyl-4,5-imidazoline (tolazoline, 'priscol') into the pulmonary artery caused a fall in pulmonary resistance, and accordingly put forward sympathetic overactivity as the fundamental cause. We also found that the pulmonary pressure fell and the oxygen concentration rose in Case 1 after the injection of tolazoline through the catheter (Table III), but the effect was so transient that estimations of output and resulting calculations of resistance could not be made. We do not agree with the hypothesis of sympathetic overactivity, for the following reasons: (1) the ganglion-blocking agent hexamethonium bromide was without effect in the two cases in which it was tried (Cases 1 and 5) (Tables V and VII), and Dresdale and his colleagues also reported that tetra-ethyl ammonium bromide had no effect; (2) Werkö and Eliasch (1952) found the resistance to be unchanged after bilateral sympathetic block; and (3) the imidazolines have a very low specificity as adrenergic blocking agents (Goodman and Gilman, 1955). Moreover, the injection of adrenaline does not cause pulmonary hypertension in normal subjects (Witham and Fleming, 1951). Cutler, Nadas, Goodale, Hickler, and Rudolph (1954) have attempted to group together all types of cases with a markedly increased pulmonary resistance, whether unexplained or secondary to congenital heart disease, under the title of the 'pulmonary vascular obstruction syndrome'. It is true that, as we have observed, many of the symptoms and signs, and much of the histological picture, are non-specific, and will be found in any patient with established pulmonary hypertension. But secondary hypertension may be sustained for many years at systemic levels with little or no progression, and this relatively benign course, in contrast with the short progressive course of the unexplained variety, must imply a fundamental difference. Attempts to group them appear, at this stage, confusing rather than helpful.

In two patients (Cases 7 and 8) Raynaud's phenomenon preceded all other symptoms, and both presented clinical evidence of arteritis elsewhere than in the lungs. The association of Raynaud's phenomenon and pulmonary hypertension has been reported by Linenthal (1942) and Taft and Mallory (1946). Both Linenthal's patients undoubtedly had progressive systemic sclerosis; both showed evidence of pulmonary fibrosis, and in the case coming to autopsy characteristic histological changes were found in the capillary walls. The

aetiology of Taft and Mallory's case was uncertain. Interstitial pulmonary fibrosis is well recognized in scleroderma, but is usually detectable radiologically (Shuford, Seaman, and Goldman, 1953; Leinwand, Duryee, and Richter, 1954), and often leads to defects of oxygen diffusion (Donald, Renzetti, Riley, and Cournand, 1951–2). The presence or absence of a diffusion defect was not established in Case 7 or Case 8, but there was no clinical evidence of scleroderma, apart from sclerodactyly, and no radiological signs of fibrosis. In Case 7 the predominant arterial lesion in the lungs and other organs was a concentric intimal sclerosis, closely resembling that found in some cases of scleroderma, and also similar to a disseminated arterial intimal fibrosis recently described by Whiteley and Wilson (1952) and distinguished by them from polyarteritis nodosa and thromboangeitis obliterans; in their patient the pulmonary vessels were not involved, and there was no definite clinical evidence of scleroderma. In our Case 7 the intimal lesion was not based on recent or old polyarteritis nodosa, though a mild arteritis was rarely encountered in the lungs and recent typical fibrinoid arteritis occurred in the renal pelvis and adrenal capsule; we are uncertain whether these two vascular lesions are simply morphological variants or distinct entities. Apart from the arterial lesions there was no definite histological evidence of scleroderma. Pulmonary hypertension has rarely been described in sclerodermatous lungs, although a case was reported by McMichael (1948) in which there was electrocardiographic evidence of right ventricular enlargement. Ellman and Cudkowicz (1954) made the interesting point that the lesions of scleroderma are confined to the pleura and interlobular septa, that is to the territory of the bronchial arteries, and doubted whether the pulmonary vasculature is ever primarily involved. It seems wiser, therefore, to regard Case 7 as an indeterminate arteritis, for it has many features which differentiate it from scleroderma. Analysis of Case 8 is difficult without histological evidence, but it appears probable that the disease began with true rheumatoid arthritis, and this accords with the positive differential agglutination test. Arteritis sometimes occurs in rheumatoid arthritis, and pulmonary involvement is frequently encountered in this disease, but no case has been reported in which the lesions in the lung have resulted in pulmonary hypertension. We have studied the pulmonary vascular dynamics in a case of rheumatoid arthritis with gross radiological signs of pulmonary involvement, and found them to be normal. A more severe arteritis may complicate rheumatoid arthritis, and Ball (1954) has reported five cases of rheumatoid arthritis associated with polyarteritis nodosa. None of his cases showed pulmonary lesions, but he concluded that the distribution, frequency, and morphology of arterial lesions in this disease were variable, ranging from a mild indeterminate arteritis to polyarteritis nodosa. The exact relation of Cases 7 and 8 to each other and to the better-known syndromes of connective-tissue disease remains uncertain, but both may be reasonably regarded as examples of pulmonary arterial disease occurring as part of generalized arteritis of indeterminate type.

Patients 9 and 10 differed from the others, for cyanosis was earlier and more marked, and both had unusually large hearts; moreover in Case 9, in which it

was possible to weigh the ventricles separately, there was a slight left ventricular hypertrophy. The striking findings in the lungs of both patients, found in no other case, were large, thin-walled bronchopulmonary anastomotic vessels. There are two possible interpretations of this finding: (1) The anastomotic vessels may be primary, the hypertension developing as a consequence of a prolonged increase in pulmonary blood-flow. This situation may be regarded as analogous to the patent ductus arteriosus complicated by pulmonary hypertension. The absence of such vessels in our other cases, and in reported cases of secondary pulmonary hypertension, favours this interpretation. (2) The anastomotic vessels may be an unusual response to obstruction to flow through the pulmonary artery. There is some support for this interpretation in Case 9, for, in the two blocks in which the anastomosis was proved, the pulmonary artery was obstructed proximal to it, and Liebow and his colleagues (Liebow, Hales, Harrison, Bloomer, and Lindskog, 1950; Liebow, 1954) have demonstrated that in dogs ligation of the pulmonary artery is rapidly followed by an increase in bronchial artery blood-flow. In Case 10, however, no occlusive lesion was seen, the pulmonary arteries being structurally normal throughout. Although the precise role of these anastomotic channels remains uncertain, their presence clearly modifies the clinical syndrome. We are not aware of any previously reported cases of this nature, although all three of the patients of de Navasquez, Forbes, and Holling (1940) and two of East's (1940) patients had slight but unexplained left ventricular hypertrophy, and greatly enlarged bronchial arteries were noted in a case described by Means and Mallory (1931–2). We have pointed out above that these channels are tortuous, and they might easily be missed unless serial sections were made. Brinton (1950) described a case of 'primary' pulmonary hypertension in which a bronchial-pulmonary arterial communication was found at the right hilum, and he argued that the increased blood-flow through the lungs was the cause of the hypertension. Brinton's case differs from ours anatomically, but both may be regarded as analogous to cases of congenital heart disease with left-to-right shunts, in which pulmonary hypertension is so frequent a complication. In another rather doubtful case, described by Wood and Miller (1938) as Ayerza's disease, injection of the aorta after death outlined the pulmonary arterial tree; unfortunately no histological examination was made. The presence of pre-capillary anastomoses in the normal lung was denied by Miller (1947), but recently it has been claimed that, in the region of small cartilaginous bronchi, short tortuous branches run distally from the bronchial arteries to form anastomoses with branches of the neighbouring pulmonary artery (von Hayek, 1953; Verloop, 1948; Tobin, 1952; Parvis, 1953–4). These anastomotic vessels possess a longitudinal muscle layer, internal to the circular muscle coat and of varying thickness. They have been called *Sperrarterien* by the Continental workers, presumably because of their supposed ability to open and close. The anastomotic vessels in our cases were different, in that they frequently possessed only a poorly developed muscle coat, and this may be the primary abnormality rather than a new growth of vessels.

Diagnosis. Unless characterized by bronchopulmonary anastomotic vessels

these cases, in which the disease is confined to the lungs, present a fairly uniform clinical syndrome of circulatory inadequacy without congestion of the lungs, and signs of pulmonary hypertension, possibly followed by congestive failure. The syndrome is easily recognizable if the possibility of the disease is appreciated. Inability to accept such symptoms and signs in the absence of overt primary disease of the heart or lungs led to a variety of initial diagnoses in our cases: nephritis in Case 1; atrial septal defect in Case 2; epilepsy in Case 3; neurosis in Cases 6 and 7; heart failure of unknown aetiology in Case 8; and pulmonary stenosis in Case 10. We have found the most difficult diagnosis to be from cases of mitral stenosis with extremely high pulmonary vascular resistance. When this complication occurs, the main obstruction to blood-flow is transferred from the mitral valve to the small muscular arteries in the lungs (Wade, 1952) resulting in a distortion of physiology comparable to that found in 'primary' pulmonary hypertension. If this differentiation is borne in mind, however, the distinction can always be made by careful analysis of the clinical and radiological data, supplemented if need be by cardiac catheterization. The value of the latter procedure is slightly lessened by the difficulty, in our experience, of obtaining reliable wedge pressure readings when there is extreme pulmonary hypertension, no doubt on account of the thickened vessels. If bronchopulmonary anastomotic channels are present the diagnosis is more difficult, and the clinical syndrome may be indistinguishable from that of certain forms of congenital heart disease with pulmonary hypertension.

Management. These cases present a difficult problem both in investigation and in treatment. Their main difficulty is maintaining blood-flow through the lungs, and for this a powerful right ventricle is required. As Salisbury (1955) has shown in dogs, the ability of the right ventricle to meet an increase in pulmonary artery pressure is dependent on coronary flow, but the cardiac output in these patients is limited, and therefore the efficiency of the coronary circulation is lessened. They will tolerate badly any procedure which may lessen cardiac efficiency or which lowers systemic blood-pressure. One of our patients died during a simple exercise test, and Schafer, Blain, Ceballos, and Bing (1956) have reported three deaths after cardiac catheterization in patients probably belonging to our first group. Death after catheterization has also been reported by Cutler, Nadas, Goodale, Hickler, and Rudolph (1954). Failure to understand the aetiology is reflected in the absence of any effective treatment. In spite of the effects claimed for intra-arterial tolazoline, we have not found oral tolazoline to be of any value; this has also been the experience of other workers (Dresdale, Schultz, and Michtom, 1951; Swallow, 1956). Patient No. 5 has derived no apparent benefit from oral dibenzyline. Other hypotensive drugs appear to be without benefit, and any drug which may cause a selectively greater fall in systemic resistance is potentially dangerous, for, as we have remarked, such patients will not tolerate a fall in coronary arterial blood-flow. Sympathectomy is also to be deprecated, for there is no evidence of a disturbance of autonomic balance. Moreover, the risk at operation is considerable; two patients reported by Inkley, Gillespie, and Funkhouser (1955), who were submitted to sympathec-

tomy, died during the induction of the anaesthetic. No effective treatment could be devised to deal with cases secondary to abnormal bronchopulmonary communications; but if, as our observations suggest, many other cases are due to a localized or generalized arteritis, steroids deserve trial, for the inherent risks of steroid therapy are more than offset by the extremely poor prognosis. We gave a short course of cortisone to two patients (Cases 7 and 8) who showed evidence of generalized arteritis, but there was no proof that this treatment affected the natural history of the disease. The value of steroids is more questionable in cases characterized by a short history, symptoms and signs of a low cardiac output, and absence of haemoptysis or cyanosis; but, as there may be an arteritis confined to the lungs, it seems reasonable to try the effect of a short course, especially if the differential agglutination test is positive.

General Conclusions

The large majority of cases of unexplained pulmonary hypertension present a characteristic clinical syndrome which is not difficult to diagnose; latterly it proved possible to use cardiac catheterization in a confirmatory rather than a diagnostic sense. Generally occurring in an apparently healthy young female subject, the syndrome consists of progressive and compelling dyspnoea, often associated with substernal discomfort or fatigue. Syncopal attacks related to effort occur in about a quarter of the cases. Cough, haemoptysis, orthopnoea, and nocturnal dyspnoea do not occur. The physical findings are confined to those of pulmonary hypertension, and cyanosis is absent or slight; there is frequently a high-coloured malar flush. On fluoroscopy the right ventricle is enlarged, the proximal part of the pulmonary arterial tree is dilated but does not show true expansile pulsation, and the peripheral lung fields are normal. There is invariably electrocardiographic evidence of right ventricular hypertrophy. Confirmation may be obtained by catheterization. The disease runs a rapid course to death from right heart failure, usually in under three years from the onset. One patient, still alive, appears to be running a much milder course. Such patients may have an arteritis confined to the lungs, but usually they do not, the increased hindrance being due to a primary contraction of terminal muscular arteries; it is this type of case which may reasonably be termed primary pulmonary hypertension. Intimal fibroelastosis and pulmonary arterial thromboses, when present, are regarded as secondary phenomena. Treatment is disappointing; vasodilators appear valueless but, as there may be an arteritis, steroids should be considered. The most difficult diagnosis is from cases of mitral stenosis characterized by an extreme increase in pulmonary vascular resistance, but careful analysis will usually serve to distinguish them.

In another group pulmonary hypertension is due to involvement of the lungs in a generalized arteritis of indeterminate type. Such patients, in addition to symptoms and signs similar to those of the previous group and referable to the pulmonary vascular disease, also have signs of digital arterial disease. Evidence of pulmonary involvement should always be carefully searched for in

patients who primarily present digital arterial lesions, and if such signs are found the prognosis is correspondingly more grave. These cases may be related to progressive systemic sclerosis. In this group steroids would seem the only hope, although our experience has not been encouraging.

In a third group, with abnormal bronchopulmonary communications, the natural history may be long, haemoptysis is common, and cyanosis and polycythaemia more pronounced. Such cases are difficult, if not impossible, to distinguish from cases of congenital heart disease with a left-to-right shunt and complicating pulmonary hypertension. We are uncertain whether the anastomotic vessels stand in causal relation to the hypertension, but suspect that they may do so.

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Summary

1. Ten cases of unexplained pulmonary hypertension are reported. The patients were between 11 and 40 years of age, and eight were female. Eight patients have died, and a detailed post-mortem examination was made in seven.

2. Six patients presented a fairly uniform clinical picture, with symptoms ascribable to a limited cardiac output and signs confined to those of pulmonary hypertension. Five died from acute or chronic failure of the right ventricle within two and a half years of the onset of symptoms, and in four a post-mortem examination was made. It is concluded that in all cases the disease was acquired and, in three cases, the increased hindrance was due to primary contraction of the terminal pulmonary arteries; in the remaining case there was an arteritis confined to the lungs.

3. Digital arterial lesions were present in two cases. Post-mortem examination in one case revealed a widespread arteritis of indeterminate type.

4. Two patients differed clinically from the others, in that they were more cyanotic and complained of haemoptysis. Both were found to have bronchopulmonary anastomotic vessels up to 200 μ in diameter.

5. The diagnosis and management are discussed. The liability to sudden death, and the risks inherent in investigatory procedures which may disturb circulatory dynamics, are emphasized.

6. Adrenergic-blocking and ganglion-blocking agents were found to be ineffectual in treatment in cases due to primary vasocontraction. Although our

own experience has not been encouraging, it is suggested that steroids should be tried in patients with evidence of arteritis, or with a positive differential agglutination test.

ADDENDUM

Since writing this paper a further case has been encountered. The patient was a married woman, 22 years of age, with one child aged four. Six months previously she had commenced with a feeling of exhaustion associated with dyspnoea and faintness on exertion; on several occasions she lost consciousness. The symptoms progressed, and after four months she suffered congestive heart failure, but this improved with treatment. On examination she was not cyanotic, and the findings were confined to those of pulmonary hypertension. Cardiac catheterization revealed a mean pulmonary arterial pressure of 80 mm. Hg, an output of 3·1 litres per minute, and a total pulmonary resistance of 2,150 dynes per sec. per cm.$^{-5}$ The systemic arterial blood was 96 per cent. saturated. It was decided to try the effect of the more specific adrenergic-blocking agent dibenzyline, and 100 mg. in 500 cc. of normal saline were infused into the pulmonary artery over a period of one hour. The mean pulmonary arterial pressure rose to 91 mm. Hg, the mean systemic pressure fell from 98 to 83 mm. Hg, and the cardiac output increased to 6·3 litres per minute. The total pulmonary resistance therefore fell to 1,100 dynes per sec. per cm.$^{-5}$ The systemic oxygen saturation fell slightly, to 90 per cent. Fifteen minutes after the conclusion of the studies and withdrawal of the catheter the patient collapsed, and died within a few minutes from what appeared to be acute right ventricular failure. The diagnosis was confirmed *post mortem*, but histological examination is still incomplete.

There seems to be no doubt that some degree of vasodilatation in the lungs was produced by dibenzyline, but the overall effect appears to have been of doubtful value. The case emphasizes the dangers inherent in the investigation of patients with this disorder.

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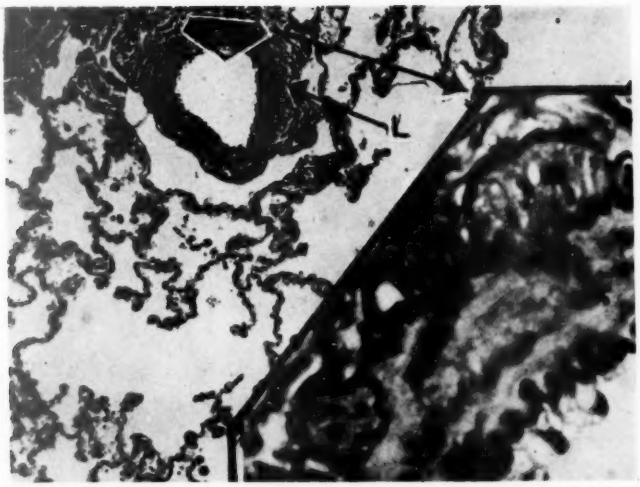

FIG. 1. Case 1. Normal alveoli; external longitudinal muscle bundles (L) (enlarged in inset) indicate hypertrophy of the pulmonary artery

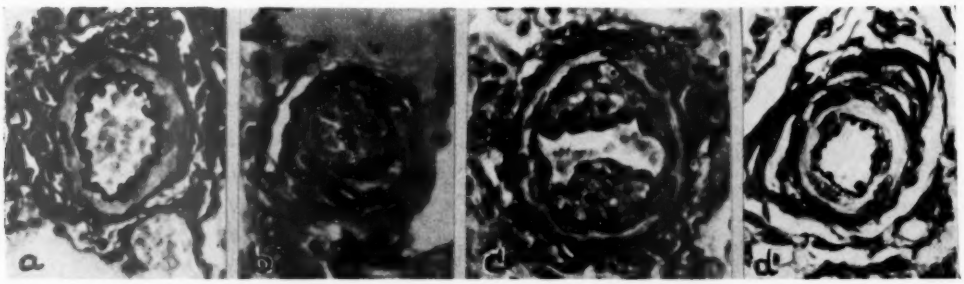

FIG. 2. Case 1. Abnormally small pulmonary arteries: (*a*), 55μ, and (*b*), 42μ, are patent; in (*c*), 63μ, internal longitudinal muscle bundles are unusually well developed; (*d*) is a normal newborn artery for comparison (×450)

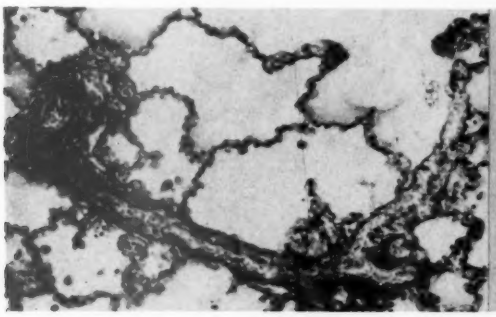

FIG. 3. Case 1. Abnormally small pulmonary artery and arteriolar branch which shows intimal thickening proximally but is normal distally (×134)

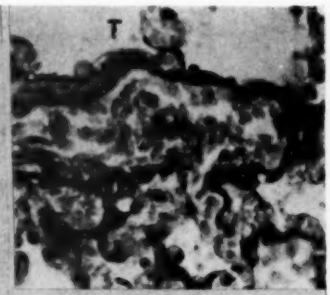

FIG. 4. Case 1. Pulmonary arteriole; at (T) intimal longitudinal muscle terminates and the vessel becomes normal; it appears short because it turns out of the plane of section (×360)

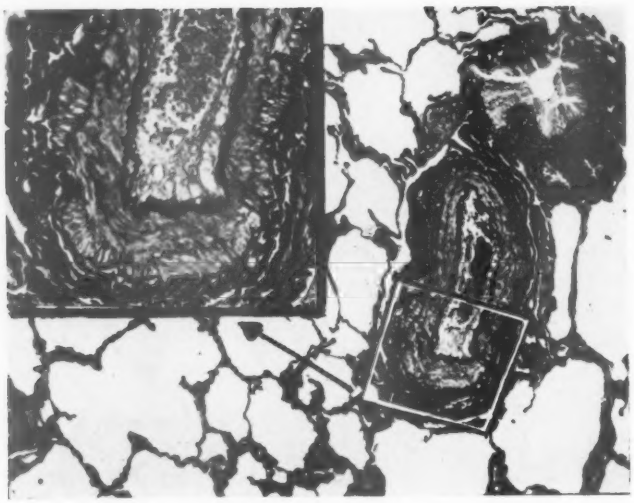

FIG. 5. Case 2. Normal alveoli and hypertrophied muscular artery, with external muscle bundles enlarged in inset

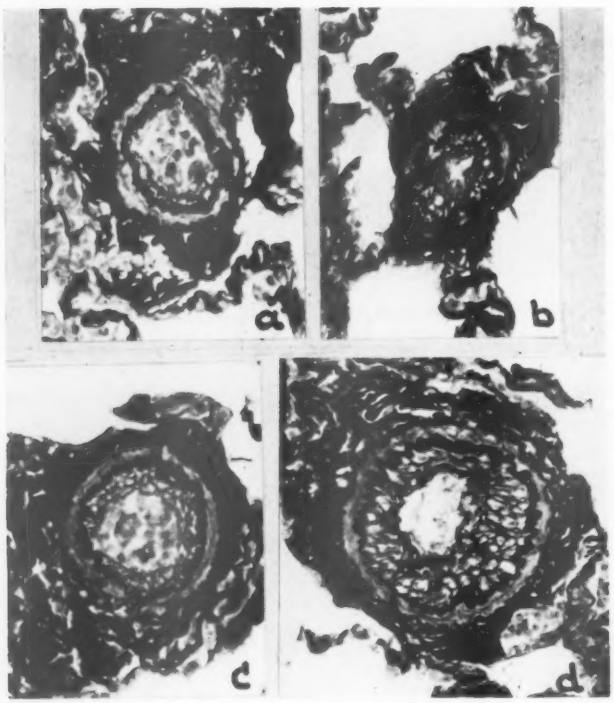

FIG. 6. Case 2. Terminal pulmonary arteries. (*a*), 60μ, is patent; (*b*), 35μ, (*c*) 75μ, and (*d*), 92μ, show degrees of luminal narrowing, mainly by longitudinal muscle ($\times$325)

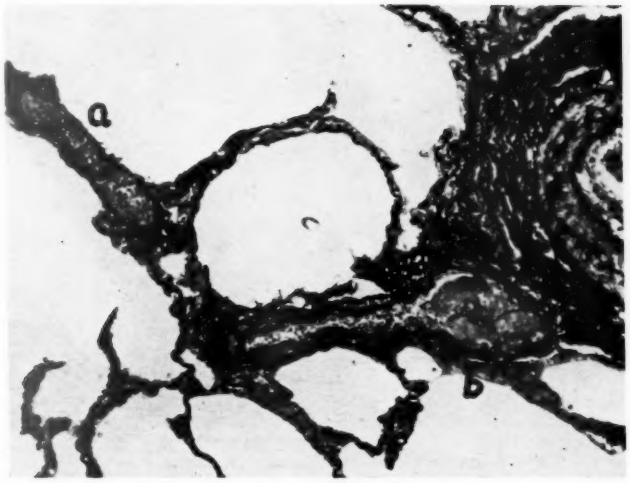

FIG. 7. Case 2. Patent pulmonary artery (p), and small arterial branch (*b*) with recent thrombosis of the dilated proximal segment; (*a*) is one of the normal arterioles joining (*b*) (×68)

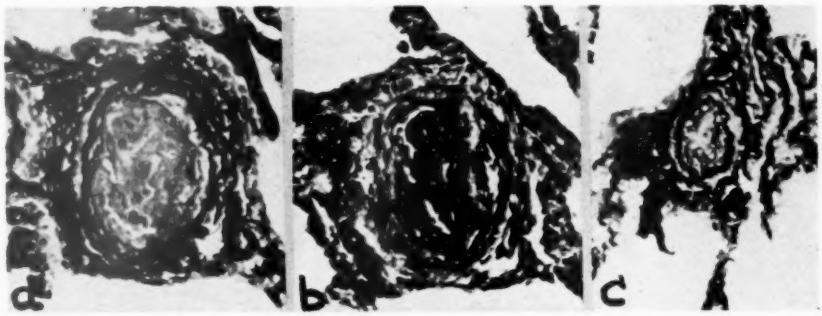

FIG. 8. Case 2. Sequence similar to that shown in Fig. 7: (*a*) segment filled with thrombus; (*b*) nearby section, to show early organization; (*c*) section of artery in (*a*) just distal to thrombosis (×216)

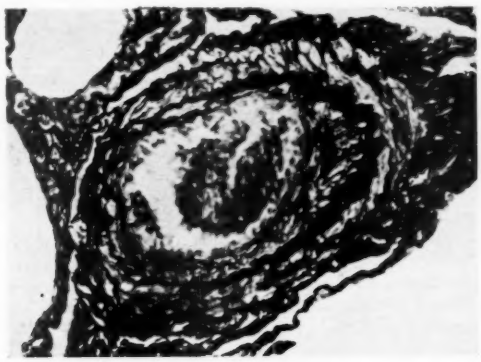

FIG. 9. Case 2. Muscular pulmonary artery showing medial defect and intimal fibrosis (×252)

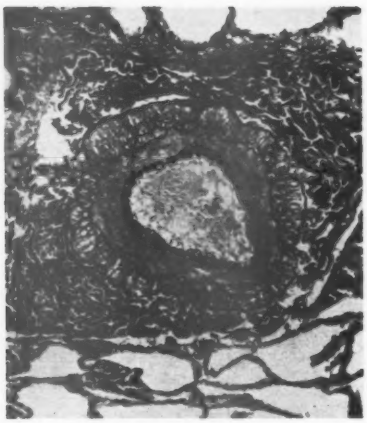

FIG. 10. Case 3. Hypertrophied pulmonary artery; external longitudinal muscle bundles form a complete coat

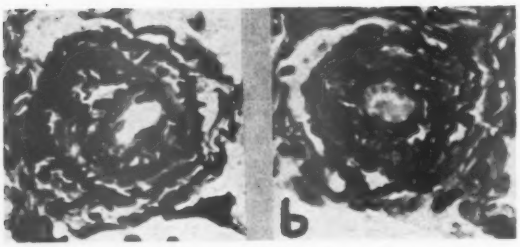

FIG. 11. Case 3. Abnormally small arteries: (*a*) ×435; (*b*) ×485

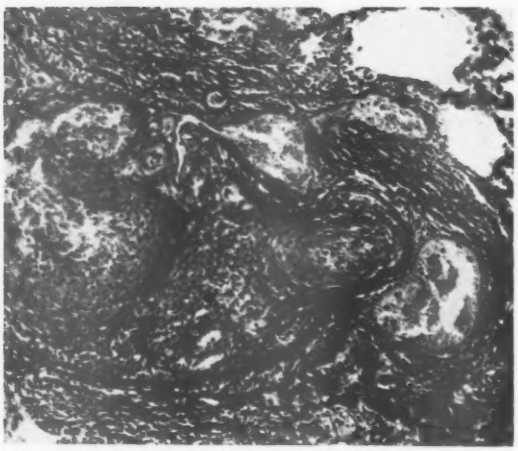

FIG. 12. Case 3. Pulmonary artery showing organized thrombus, and a transmural capillary (*c*) joining a dilated adventitial capillary (×158)

FIG. 13. Case 3. Small pulmonary artery with the lumen obliterated by dense fibrous tissue; a dilated adventitial capillary cleaves the wall (×192)

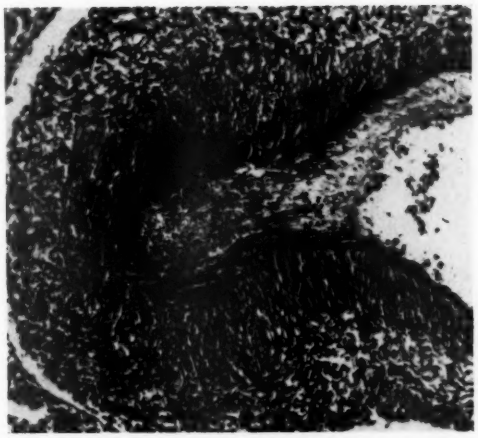

FIG. 14. Case 6. Fibrinoid arteritis (×104)

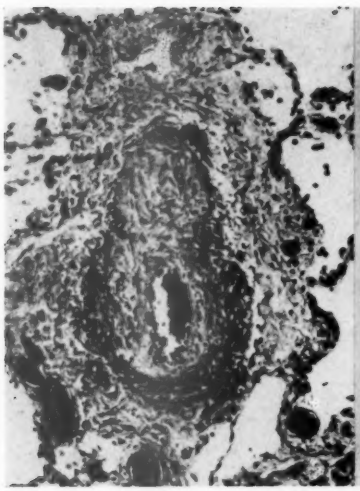

FIG. 15. Case 6. Healed arteritis showing fibrous replacement of media (×124)

FIG. 16. Case 6. Small pulmonary artery, (*a*) showing intimal fibrosis; (*b*) is a branch of (*a*), and shows mild arteritis without mural necrosis (×88)

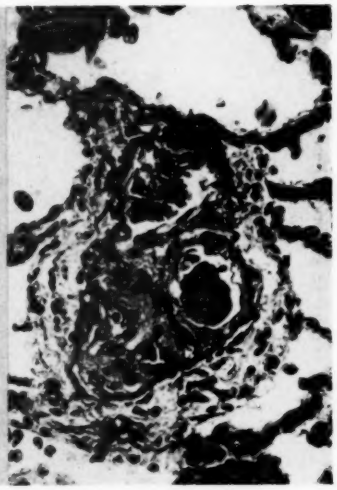

FIG. 17. Case 6. Arteriolitis: intimal swelling, thrombosis, and perivascular oedema and leucocytic infiltration in a dividing arteriole (×285)

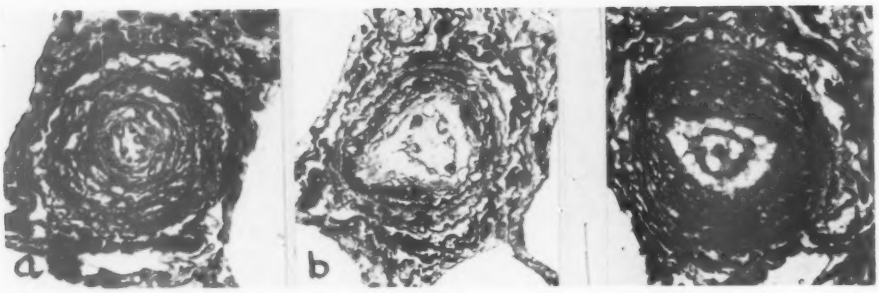

FIG. 18. Case 7. (*a*) Pulmonary artery (100 μ) showing concentric intimal fibroelastosis; (*b*) the same vessel at another level showing intimal oedema and much-reduced fibrosis (×272). Compare with Figs. 6 and 9

FIG. 19. Case 7. Intimal oedema separates endothelium from concentric intimal fibrosis (×236). Compare with Figs. 6 and 9

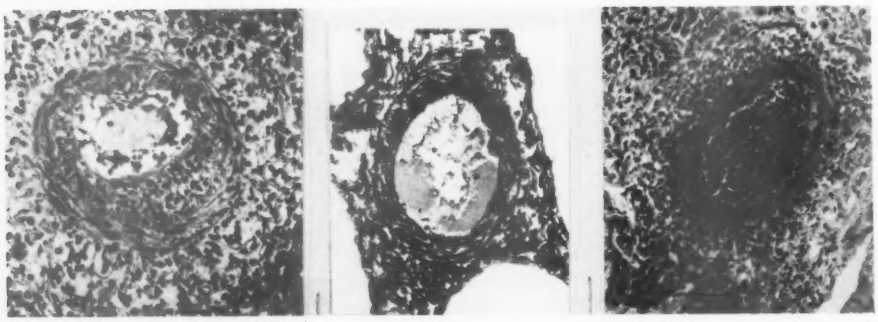

FIG. 20. Case 7. Mild indeterminate arteritis in a pulmonary artery

FIG. 21. Case 7. Subintimal serous coagulum in a pulmonary artery (×162)

FIG. 22. Case 7. Fibrinoid arteritis in the adrenal capsule (×162)

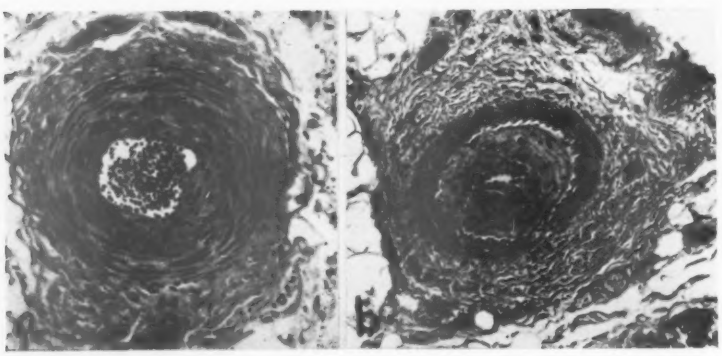

FIG. 23. Case 7. Concentric intimal fibrosis in otherwise normal vessels: (*a*) a palmar artery; (*b*) a pancreatic artery (×176)

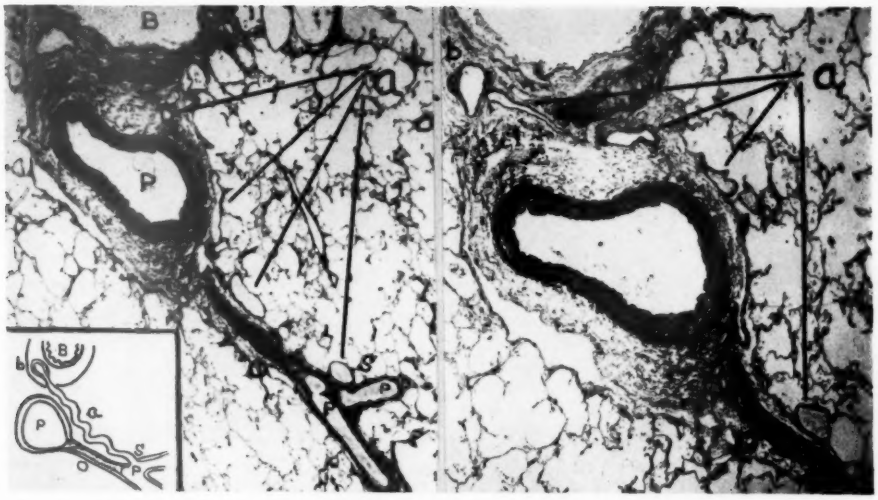

FIG. 24. Case 9. Two sections of a bronchopulmonary anastomosis. Bronchus (B); bronchial artery (*b*), pulmonary artery (P) with obstructed segment (O). The thin-walled anastomotic vessel (*a*) is about to join the pulmonary artery at (S). Inset: diagram of anastomosis based on serial sections

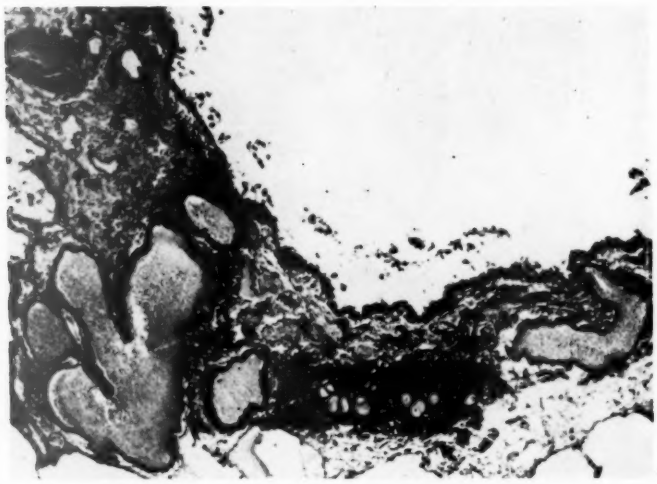

FIG. 25. Case 9. Dilated varicose vessels in the wall of a cartilaginous bronchus (×68)

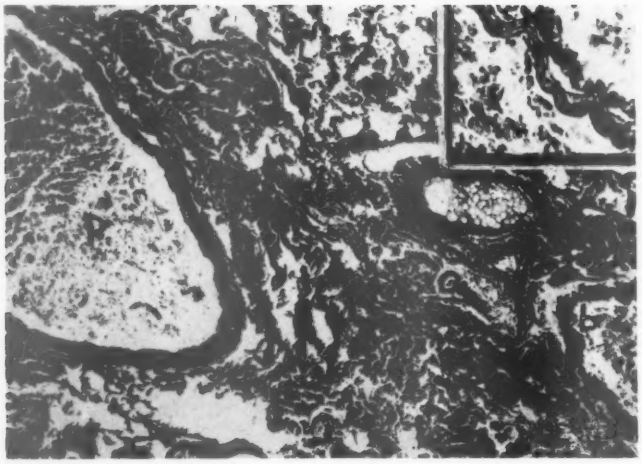

FIG. 26

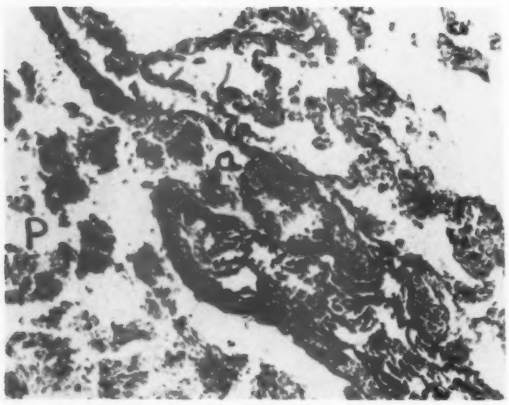

FIG. 27

FIGS. 26 and 27. Case 10. Two sections of a bronchopulmonary anastomosis. Fig 26: the anastomotic vessel (*a*) leaves the bronchial wall (*b*) and courses alongside the pulmonary artery (P); wall of (*a*) enlarged in inset. Fig. 27 shows the opening of the anastomotic vessel into the pulmonary artery

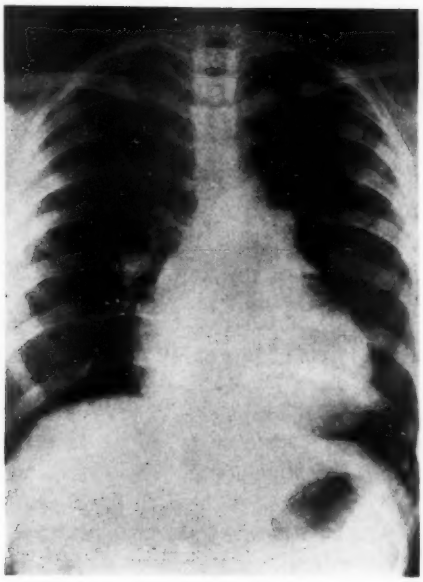

FIG. 28*a*

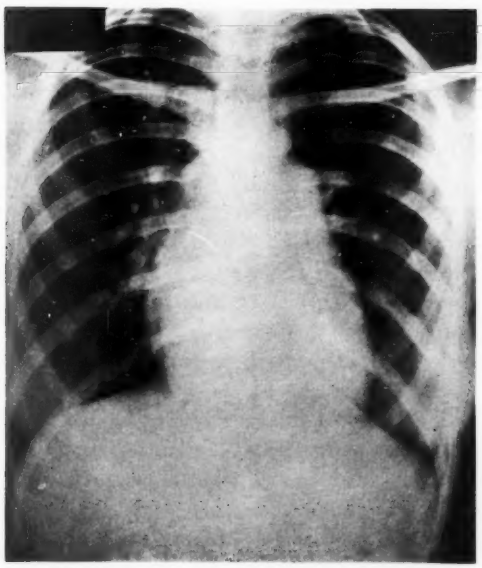

FIG. 28*b*

FIG. 28. Chest film in Case 1 (*a*) and Case 2 (*b*). Note the proximal dilatation of the pulmonary arterial tree and, by contrast, the normal peripheral lung fields

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THE VALUE OF THE ORAL GLUCOSE TEST IN THE DIAGNOSIS OF PANCREATIC FROM IDIOPATHIC STEATORRHOEA [1]

By R. GADDIE, GARFIELD THOMAS, NADYA SMITH, and J. M. FRENCH

(From the Departments of Biochemistry, General Hospital and Queen Elizabeth Hospital, and the Department of Medicine, University of Birmingham)

Many cases of pancreatic steatorrhoea present a clinical picture which is indistinguishable from idiopathic steatorrhoea, and special investigations are necessary to differentiate between the two conditions. The simplest test is examination of the faeces microscopically and chemically for undigested and unabsorbed fat and protein, and an estimation of the ratio of split to unsplit fat. Undigested and unabsorbed fat and protein are found in both conditions, however, and for various reasons the ratio of split to unsplit fat may be entirely unrepresentative of the presence or absence of pancreatic secretion (Andersen, 1945; Cooke, Elkes, Frazer, Parkes, Peeney, Sammons, and Thomas, 1946; Weijers and van de Kamer, 1953). The most reliable method of differentiation is to intubate the patient under radiological control, and measure the activity of amylase, lipase, and trypsin in several specimens of duodenal juice. Although not difficult, the intubation frequently proves tedious, the analytical procedures are time-consuming, and the necessary facilities for both may not always be available. Any investigation which would aid the differentiation without resort to duodenal intubation would therefore be welcome.

It is recognized that patients with chronic pancreatitis may gradually develop diabetes mellitus, and that carbohydrate intolerance may show itself temporarily in early stages of the disease. Many cases of steatorrhoea of pancreatic origin, however, give no clinical history suggestive of pancreatitis, though examination of the pancreas at laparotomy or *post mortem* may show diffuse fibrosis of the gland. Diabetes mellitus found in such cases suggests that the routine examination of glucose tolerance in steatorrhoea would assist differentiation of the cases of pancreatic insufficiency, especially from those of idiopathic steatorrhoea and sprue, in which 'flat' glucose curves are usually seen (Thaysen, 1932; Bennett, Hunter, and Vaughan, 1932; Fairley, 1936–7). Although this possibility was first pointed out many years ago (Thaysen, 1926), the published reports are too few to determine the type of curve to be expected in pancreatic steatorrhoea, the frequency with which abnormal curves are encountered in this condition, and the value of the test in diagnosis. The object of the present report

[1] Received July 2, 1956.

is to present data from cases of steatorrhoea which relate the results of pancreatic enzyme estimation to those of the glucose-tolerance test. The observations show that the glucose-tolerance test is sufficiently characteristic to be of assistance in diagnosis.

Patients and Methods of Investigation

Twenty persons with steatorrhoea were examined. In 10 the steatorrhoea was pancreatic, and in 10 idiopathic (see Table). In all cases the presenting symptom was diarrhoea. The diagnosis was established by the following special investigations: (1) Fat-absorption was measured on a controlled fat intake, faecal fat being measured by the method of van de Kamer, ten Bokkel Huinink, and Weijers (1949). (2) Duodenal intubation was carried out under radiological control with a radio-opaque tube, and juice aspirated from the second or third part of the duodenum at intervals of a few minutes, without stimulation of pancreatic secretion by mecholyl or secretin. Only those specimens which were clear and had a pH greater than 6·0 were used. All specimens contained yellow bile-pigment. Amylase, lipase, and trypsin activities were determined by the methods of Ågren and Lagerlöf (1936), Sammons (Anderson, Frazer, French, Gerrard, Sammons, and Smellie, 1952), and Charney and Tomarelli (1947) respectively. (3) Microscopic examination of the faeces. (4) Blood counts and estimation of red-cell haemoglobin concentration and mean cell-volume. (5) Radiological examination of the gastrointestinal tract with the barium meal.

Pancreatic disease. Ten of the patients, who were diagnosed as suffering from steatorrhoea of pancreatic origin, showed diminished fat-absorption (see Table). Pancreatic enzyme activities were absent or grossly deficient in all samples of duodenal juice. The faeces on microscopic examination contained abnormal amounts of undigested meat-fibres and fat. The fat was sometimes in globular form, but more often in masses of soaps and fatty acids, as seen in idiopathic steatorrhoea. Starch was rarely seen. Three patients (Cases 1, 2, and 3) had had diarrhoea since early childhood, and, although only one of them had bronchiectasis, a presumptive diagnosis of cystic fibrosis of the pancreas was made. Laparotomy was performed in Case 4, and the pancreas showed numerous firm areas consistent with a quiescent chronic pancreatitis. Two patients (Cases 6 and 9) had diabetes mellitus controlled by insulin and diet. Calcification of the pancreas was present only in Case 7.

Idiopathic steatorrhoea. The 10 patients who were diagnosed as having idiopathic steatorrhoea showed diminished fat-absorption (see Table). Pancreatic enzyme activities in the duodenal juice were normal. In the faeces fat was seen microscopically in the form of fatty acids and soaps, and there was frequently an excess of meat-fibres, though in a partly digested state. Starch was seen occasionally. An opaque meal with ordinary barium showed flocculation of the barium sulphate and dilatation of the small intestine. All these patients were anaemic, the anaemia being macrocytic in seven, and hypochromic and microcytic, with anisocytosis, in the remaining three, who were women (Cases 11, 14,

Fat Balance Data and Glucose Tolerance in Pancreatic and Idiopathic Steatorrhoea

				Fat balance data				Blood-sugar (mg./100 ml.) after 50 gm. of oral glucose					
	Case number	Age (years)	Sex	Mean daily intake (gm.)	Mean daily excretion (gm.) (normal less than 5 gm.)	Duration of test (days)	Absorption (normal more than 90%)	Fasting	½ hr.	1 hr.	1½ hrs.	2 hrs.	2½ hrs.
Pancreatic insufficiency:													
	1	13	F	50	18·6	10	62·8	112	177	214	190	179	123
	2	18	M	50	30·9	10	38·2	70	160	183	105	65	129
	3	18	M	50	36·8	6	26·4	55	132	183	219	185	
	4	33	F	50	11·3	10	77·4	114	166	184	180	132	
	5	44	M	50	9·6	5	80·8	116	193	271	273	255	
	6*	48	M	50	23·6	5	52·8	235	255	390	395	390	385
	7	48	M	70	20·0	5	71·4	84	206	262	207	192	135
	8	52	M	50	36·4	10	63·6	139	184	238	273	301	73
	9*	55	F	50	46·6	5	6·8	299	391	430	490	441	
	10	61	M	50	32·0	4	36·0	98	173	216	219	166	
Idiopathic steatorrhoea:													
	11	29	F	50	18·6	10	62·8	80	85	100	97	88	81
	12	36	M	70	15·3	10	78·1	85	95	105	121	125	130
	13	36	F	50	7·5	10	85·0	101	120	120	115	120	
	14	39	F	50	15·6	5	68·8	90	130	120	90	95	95
	15	50	F	50	37·7	10	24·6	71	105	108	110	110	
	16	52	M	50	8·4	10	83·2	85	85	118	140	120	
	17	53	F	75	36·3	10	51·2	83	83	83	90	110	
	18	54	M	50	6·0	10	88·0	90	90	110	130	115	
	19	56	M	50	21·1	10	57·8	70	72	72	92	70	60
	20	57	M	50	28·1	10	43·8	72	78	105	80	63	80

* Patient receiving insulin except for morning of test.

and 17). Only in four cases was there evidence of coeliac disease in childhood (Cases 13, 14, 16, and 17).

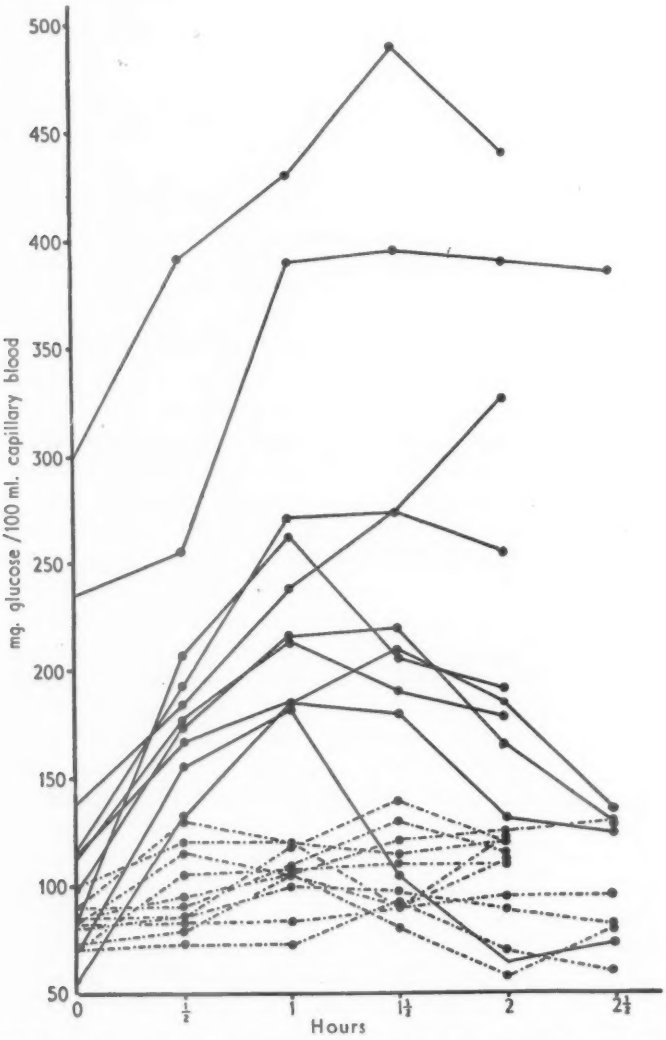


FIG. 1. Individual blood-sugar curves after 50 gm. glucose by mouth in 10 patients with pancreatogenous and in 10 with idiopathic steatorrhoea (continuous and broken lines respectively).

Glucose-tolerance tests. Glucose in capillary blood was determined by the method of Hagedorn and Jensen (1923), with the patient fasting, at half-hourly intervals after giving 50 gm. of glucose in 200 to 300 ml. of water. Insulin was withheld on the morning of the test from the two patients who were receiving it.

Results (Figs. 1 and 2)

In pancreatic insufficiency the fasting blood-sugar was above the normal range in three patients, and the peak of the curve was above the normal range in all.

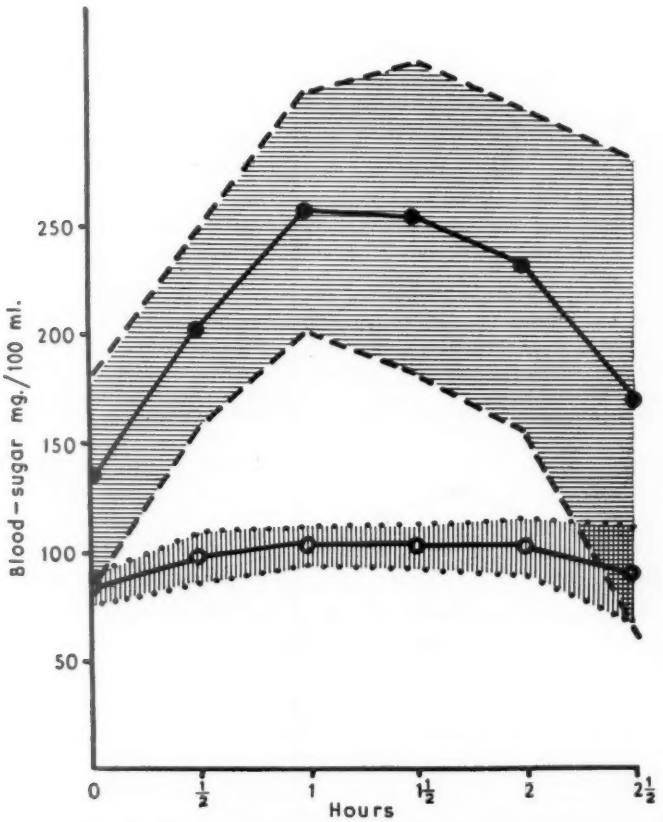
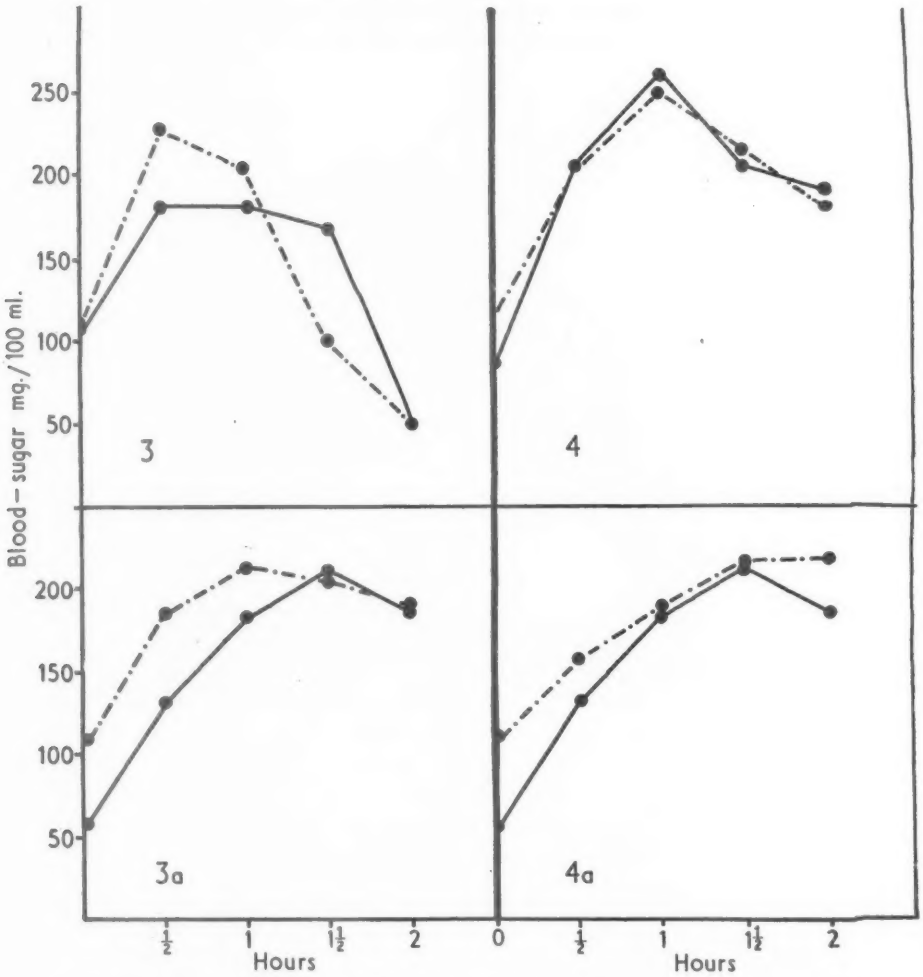


FIG. 2. Glucose tolerance: mean curves constructed from the results in Fig. 1. Upper curve pancreatic, lower curve idiopathic steatorrhoea (hatched areas show limits of twice the standard deviation of the mean).

The return of the blood-sugar to the fasting level was delayed beyond the normal time of one and a half to two hours in all cases except one (Case 2). In the cases of idiopathic steatorrhoea the rise in the blood-sugar level was delayed and depressed. The individual curves are shown in Fig. 1, and the mean curves of the two groups in Fig. 2. The difference between the means is significant. Abnormal elevation of the curve may be seen in carbohydrate starvation. Four patients with pancreatic insufficiency were therefore examined on a second occasion, two the morning after a four-day period during which 50 gm. of glucose had been

taken orally before breakfast each morning (total 200 gm.), and two after the institution of pancreatin therapy. Comparison of the results of the second



FIGS. 3, 3*a*. Pancreatogenous steatorrhoea. Glucose-tolerance curves in two cases before (continuous lines) and immediately after (broken lines) a four-day period in which 50 gm. of glucose was given each morning in addition to normal meals. There was no flattening of the curves in the second examination, as would be expected if the initial high curves were due to carbohydrate starvation.

FIGS. 4, 4*a*. Pancreatogenous steatorrhoea. Glucose tolerance curves in two cases before (continuous lines) and after (broken lines) a period of pancreatin therapy. There is no change in the type of curve.

examination with those of the first showed no essential difference in any of the four cases (Figs. 3, 3*a*, and 4, 4*a*).

Discussion

In idiopathic steatorrhoea, intubation studies have shown that 'flat' glucose tolerance curves are associated with delayed absorption from the small intestine (Groen, 1938; Taylor and Wightman, 1952; Frazer, French, Thomas, and Thompson, 1952). This delay may be due to excessive secretion of mucus and diminished intestinal motility. By contrast, in pancreatic disease, malabsorption is due to defective digestion from diminished enzyme secretion; there should be no delay in the absorption of substances which have no need to undergo digestion, such as glucose. The observations in the present series showed, in the latter condition, a rise in blood-sugar levels which was greater than normal, and a delay in return to the fasting levels. There are several possible reasons for this course of events.

Damage to islet tissue in pancreatitis is well recognized. Four of the curves were frankly diabetic, and two of these patients were receiving insulin, as their diabetes had been diagnosed some months before discovery of steatorrhoea and the associated defect in external pancreatic secretion. In these four cases, therefore, absence of external pancreatic secretion combined with a diabetic state would suggest widespread pancreatic destruction or atrophy, and the excessive rise in blood-sugar levels could have been due to damage to the islets of Langerhans.

Starvation and a low carbohydrate intake may diminish carbohydrate tolerance and thus modify the shape of the curve (MacLean, 1926; Sweeney, 1927; Himsworth, 1935–6). The effect of starvation is not seen unless the period of fasting is more than 15 hours (Staub, 1922): it is associated with low fasting blood-sugar levels. As the longest period of fasting in the present series was overnight (12 to 15 hours) and low fasting levels were not a feature, starvation was not considered a factor in diminishing carbohydrate tolerance. The patients in the pancreatic group were on a generous normal diet containing 50 to 70 gm. of fat, 80 to 100 gm. of protein, and about 300 gm. of carbohydrate. The lack of pancreatic digestion would, however, be responsible for some delay in the digestion of starch, and, although intake was adequate, carbohydrate may not have been absorbed, or may have been absorbed more slowly than normal, giving a relative insufficiency. Against this view is the fact that the glucose-tolerance tests repeated during the regular administration of pancreatin with meals, and after extra glucose, were unchanged (Figs. 3 and 4). It seems unlikely, therefore, that lessened carbohydrate intake, relative or actual, was responsible for the diminished tolerance.

Hepatic damage may cause diminished tolerance. Of the 10 cases of pancreatic insufficiency, liver function tests were carried out in two, and found to be normal (Cases 7 and 10). The contribution of liver damage to such curves remains in doubt.

Unusually rapid absorption may take place in the absence of pyloric control (for example, after gastrectomy) and the blood-sugar level may thus rise to excessive heights. The rise is steep, and is followed quickly by a precipitous fall,

often to levels which cause hypoglycaemic symptoms. This type of curve may be reproduced by instillation of glucose directly into the duodenum (Evensen, 1942), and is quite unlike the curves of pancreatic steatorrhoea recorded here. One patient (Case 4) was studied by an intraduodenal drip technique, and the rate of rise was normal, but the blood-sugar level remained elevated later, as in the oral test. As pyloric control was intact in our patients, it seems unlikely that rapid absorption plays any part.

The frequency with which abnormal curves are seen in pancreatogenous steatorrhoea does not appear to be established. Numerous observations have, however, been made in patients in whom a diagnosis of chronic pancreatitis has been established either by clinical history or at laparotomy. For instance, of the larger series, Comfort, Gambill, and Baggenstoss (1946) studied 29 patients, and found that six had diabetes and steatorrhoea, four had diabetes only, and two had steatorrhoea without diabetes. Somewhat similar observations were noted by Maimon, Kirsner, and Palmer (1948) in a study of 20 cases, and by Snell and Comfort (1941) in 18 patients with pancreatic lithiasis. Steatorrhoea was, however, assessed only in those patients in whom it was suspected on clinical grounds, and even then by stool microscopy or by percentage of fat in the faeces, procedures which have both been found to be unreliable when controlled by fat-balance experiments (Weijers and van de Kamer, 1953). Thus the relationship of steatorrhoea to glucose tolerance has not been clearly shown even in chronic pancreatitis. Pancreatogenous steatorrhoea is not confined, however, to patients with symptoms of pancreatitis, or to those in whom pancreatic calcification can be demonstrated by X-ray. There may be no suggestion in the clinical history that the pancreas is involved. When an excess of faecal fat is found in a case of diarrhoea, it is essential that pancreatic insufficiency be excluded. Although Snell and Comfort examined the enzymes in seven of their patients with lithiasis, and found them absent in two, they did not record the relation of this to their other findings; the fullest record seems to be that of Thaysen (1926), who compared four patients diagnosed as suffering from idiopathic steatorrhoea with five suffering from pancreatogenous steatorrhoea. The former showed normal glucose curves; of the latter, one was diabetic, and the other four showed normal fasting blood-sugar levels, but a diabetic curve after the administration of glucose. He examined the duodenal juice in three cases of each condition, and found the enzymes to be 'normal, or diminished' in both the idiopathic and the pancreatic cases; he regarded the investigation as in no way helpful in establishing the diagnosis. As the demonstration of normal and deficient external pancreatic secretion in idiopathic and pancreatic steatorrhoea respectively is an essential criterion of diagnosis, it is not certain exactly to what type the cases studied by Thaysen belonged. Confusion may arise from a third condition, 'diarrhoea of diabetes' (Bargen, Bollman, and Kepler, 1936; Sheridan and Bailey, 1946), which is a complication of established diabetes mellitus, associated with neuropathy in the majority of cases. There may be an excess of faecal fat, probably due to intestinal hurry, but the external pancreatic secretion is normal (Malins and French, 1956). It seems clear from the various other case reports

that, although the value of the study of carbohydrate tolerance has been observed, no body of data has been accumulated by any one group of workers to indicate how much reliance may be placed upon the investigation as an aid in the diagnosis of pancreatic steatorrhoea.

All the patients with pancreatogenous steatorrhoea investigated by us presented diarrhoea as the main symptom, and only one had a clinical history to suggest pancreatitis. The detection of steatorrhoea led to the examination of the external pancreatic secretion, and insufficiency was established by assay of enzymic activity in each case. In three cases the most likely diagnosis seemed to be cystic fibrosis of the pancreas, and in two chronic pancreatitis—in one because of calcification. The basic disorder in the remainder was not established. The study of glucose tolerance suggested that, whatever the aetiology of the pancreatic disorder in these patients, by the time the changes in the pancreas were sufficiently advanced to give evidence of defective external pancreatic secretion there was an impairment of carbohydrate tolerance. Although the exact mechanism which caused the impairment was in doubt, the ultimate development of diabetes in some of them suggested deficient islet tissue as the most important element, because the association of chronic pancreatitis with generalized fibrosis or atrophy of the gland is so well established. Glucose-tolerance curves in idiopathic steatorrhoea are frequently flatter than normal, and the finding has some diagnostic importance. The finding of such a high proportion of elevated glucose curves in pancreatic steatorrhoea, as observed in this study, clearly enhances the value of the glucose-tolerance test as a diagnostic procedure.

We are glad to acknowledge the helpful co-operation of the physicians of the United Birmingham Hospitals. Dr. H. G. Sammons kindly carried out pancreatic enzyme estimations in several cases. We are grateful for financial assistance from the Endowment Research Fund of the United Birmingham Hospitals, the Mackenzie Mackinnon Trust, and the Medical Research Council.

Summary

Glucose tolerance was examined in 20 cases of steatorrhoea, 10 of pancreatic, and 10 of idiopathic origin.

In all the pancreatic cases the glucose tolerance was impaired, and four were frankly diabetic. The curves contrasted sharply with the 'flat' curves observed in the patients with idiopathic steatorrhoea. These findings confirm the value of glucose-tolerance tests in separating the two groups of steatorrhoea.

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MYELOSCLEROSIS[1]

A Clinicopathological Study

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With Plates 17 and 18

'To achieve accuracy of diagnosis, a definition of the disease is an essential requirement, and to provide one which will admit every case, and yet not include any example of other conditions, is difficult.' R. H. COWDELL (1954)

MYELOSCLEROSIS is a disease of adults of unknown aetiology, characterized by a slowly progressive splenomegaly, a leucoerythroblastic blood picture, and infiltration of bone-marrow by fibrous tissue and cancellous bone. Myelofibrosis shows a diffuse fibrosis of the bone-marrow without proliferation of bone. A detailed pathological study of myelosclerosis was made by Vaughan (1936), and probably similar cases were described by Heuck (1879). It is almost certain that a large number of cases have been described under the confusing titles of aleukaemic megakaryocytic myelosis, myeloid megakaryocytic hepatosplenomegaly, agnogenic myeloid metaplasia, chronic non-leukaemic myelosis, and osteopathia condensans disseminata. Other conditions may give rise to myelosclerosis and leucoerythroblastic anaemia, for example: metastatic carcinoma of the marrow from primary sites in lung, prostate, breast, thyroid, stomach, and adrenals; various forms of leukaemia; polycythaemia vera; multiple myelomatosis; Hodgkin's disease; Gaucher's disease; osteitis deformans; osteitis fibrosa cystica; osteomalacia; syphilis; and the results of toxic agents, such as phosphorus, fluorine, arsenic, benzene, aniline, and irradiation. Erf and Herbut (1944) gave a very complete list of conditions in which diffuse or focal myelosclerosis has been described, and Crail, Alt, and Nadler (1948) reported several cases in which tuberculosis was found and considered to be aetiologically significant in its production.

Albers-Schönberg disease (marble bone disease, osteopetrosis) appears in a much younger age-group, pathological fractures are commonly seen, and the skeletal radiograms are very characteristic. It appears to be an entirely different disease from myelosclerosis, and has been well reviewed by Griffiths (1955). Until recently the splenomegaly of myelosclerosis was thought to be due to the development of extramedullary haemopoiesis, a compensatory

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mechanism dependent upon the degree of marrow failure; this view was compatible with the high mortality following splenectomy reported by Hickling (1937), 15 of whose 27 patients died within the first four weeks after operation. This high mortality no doubt influenced many in regarding myelosclerosis as an absolute contra-indication to splenectomy; thus Whitby and Britton (1953) said 'splenectomy is valueless and usually fatal, as the enlargement of the spleen is compensatory, and this organ is usually an important site of haemopoiesis'. There has been a growing tendency in recent years to classify myelosclerosis as simply a variant of chronic myeloid leukaemia. Heller, Lewisohn, and Palin (1947), Rosenthal (1950), Dameshek (1951), Robson (1953), and Hutt, Pinniger, and Wetherley-Mein (1953) have considered myelosclerosis, chronic myeloid leukaemia, polycythaemia vera, megakaryocytic leukaemia, and erythroleukaemia as related disorders of proliferative activity of the bone-marrow cells. Dameshek (1951) stated that 'these various conditions—the myeloproliferative disorders—are all somewhat variable manifestations of proliferative activity of the bone-marrow cells, perhaps due to a hitherto undiscovered stimulus. This may affect the marrow cells diffusely or irregularly with the result that various syndromes, either clear-cut or transitional, result. As a group it is difficult to draw any clear-cut dividing lines, in fact so many "transition" forms exist that one may with equal reasonableness call a single condition by at least two different terms.'

Wyatt and Sommers (1950), after a detailed study of some 30 cases of myelosclerosis, formed an entirely different conception, and drew pathological analogies between myelosclerosis and hepatic cirrhosis, both being morphological entities without aetiological unity. They said that in both diseases toxic agents and metabolic deficiencies cause necrosis of parenchyma, followed by reparative hyperplasia of surviving cells, and that continuance of parenchymal damage leads to overgrowth of the stromal cells, and finally inadequate organ function progressing to failure and death. They proposed five major aetiological groups of myelosclerosis, due to (1) extrinsic toxic agents, for example, benzol; (2) disorders of liver function; (3) endocrine diseases; (4) chronic haemorrhage or haemolysis; and (5) cardiovascular disease. Wintrobe (1951) also considered that there was no sound basis for assuming that myelosclerosis is a variety of leukaemia. In view of these conflicting opinions on the aetiology of myelosclerosis and its relationship to chronic myeloid leukaemia and other proliferative marrow disorders, we thought it profitable to study again the clinical and pathological findings in 28 cases of myelosclerosis which have been under our observation for periods varying from six months to six years, and to discuss the difficulties, when they arose, in distinguishing myelosclerosis from chronic myeloid leukaemia and polycythaemia vera.

Symptoms and Signs

The 28 cases were equally distributed between the sexes, and the age of the patients at the time of clinical diagnosis is shown in Fig. 1; the majority were

first diagnosed when aged 50 to 70 years. No exposure to toxic agents, such as benzol, described by Wyatt and Sommers (1950) as capable of producing this condition, was discovered. In two of our patients polycythaemia vera had preceded the appearance of myelosclerosis, by 17 years in Case 18 and by 10 years in Case 26; this sequence has been noted by Lawrence, Berlin, and Huff (1953),

TABLE I

Age, Sex, Occupation, Duration of Disease, Associated Conditions, and Degree of Splenomegaly and Hepatomegaly in 28 Cases of Myelosclerosis

Case number	*Age (years)*	*Sex*	*Occupation*	*Splenomegaly*	*Hepatomegaly*	*Duration of disease (months)*	*Associated conditions*
1	52	M	Riveter	+++	..	(Dead) 28	..
2	44	M	Stove enameller	+++	+	(Dead) 20	Rectal bleeding
3	51	M	Motor driver	+++	+	(Alive) 15	..
4	59	M	Postman	+++	+	(Dead) 45	..
5	72	M	Coal miner	+++	+	(Dead) 19	..
6	53	M	Bleacher	+++	..	(Dead) 36	..
7	62	M	Tractor driver	+++	..	(Dead) 6	Emphysema
8	72	F	Housewife	++	..	(Alive) 2	Gastric polyp
9	38	F	Housewife	++	..	(Dead) 36	..
10	64	F	Housewife	+++	..	(Dead) 24	..
11	42	F	Housewife	+++	..	(Alive) 14	..
12	66	F	Housewife	++	..	(Alive) 18	..
13	65	M	Gardener	+++	+	(Alive) 6	Rectal bleeding
14	61	F	Housewife	+++	..	(Alive) 48	Gall-stones
15	52	M	Furniture salesman	+++	..	(Dead) 180	..
16	60	M	Publican	+++	..	(Dead) 17	..
17	48	F	Housewife	++	+	(Alive) 6	..
18	67	M	Electrical engineer	+++	+	(Dead) 204	Polycythaemia vera
19	51	F	Housewife	++	..	(Dead) 48	..
20	53	M	Labourer (cotton mill)	+++	..	(Dead) 44	..
21	69	F	Housewife	+++	+	(Dead) 51	..
22	61	F	Housewife	+++	..	(Dead) 37	Ovarian cyst
23	56	F	Housewife	+++	..	(Dead) 12	Diabetes mellitus
24	66	F	Housewife	+++	..	(Dead) 12	..
25	52	M	Salt worker	+++	..	(Dead) 42	..
26	65	M	Bank cashier	+++	+	(Alive) 10	Polycythaemia vera
27	46	F	Housewife	++	..	(Alive) 36	..
28	52	F	Housewife	++	+	(Alive) 10	..

and by Steinfield and Beizer (1954). It is difficult to estimate accurately the duration of myelosclerosis, because many of the patients who reported slight symptoms had massive splenomegaly, and could very well have had the disease for many years. Thus our survival times are strictly minimal, and have been taken from the time when the diagnosis was established. It can be seen from Table I that half the patients survived for periods longer than two years, and two such patients are still living after 36 and 48 months. Hickling (1953) and Robson (1953) described a high incidence of peptic ulcer and gout in their series, but only one of our patients (Case 26) suffered from gout, which followed X-ray treatment given for polycythaemia vera. Occult bleeding was found in three patients, and

in one was due to a benign gastric polyp; in the remaining two radiology failed to demonstrate a gastrointestinal lesion. We have observed three modes of clinical presentation in our patients with myelosclerosis.

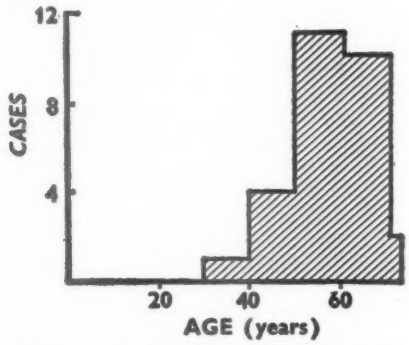

FIG. 1. Age distribution of 28 cases of myelosclerosis when first diagnosed.

1. *Asymptomatic group (three cases).* The splenomegaly was discovered accidentally on routine medical examination for some quite unrelated condition in Cases 11, 12, and 14.

Example: Case 14. Four years ago a housewife of 61 years sought medical advice for a urinary infection, and on examination was found to have massive splenomegaly. She complained of no previous symptoms that could be attributed to it. Blood examination showed haemoglobin 12·4 gm. per 100 ml. (84 per cent.), red cells 4,130,000 per c.mm., and white cells 11,000 per c.mm. (polymorphs 63 per cent., lymphocytes 14 per cent., monocytes 3 per cent., eosinophils 0·5 per cent., basophils 0·5 per cent., myeloblasts 1·5 per cent., promyelocytes 2 per cent., myelocytes 4·5 per cent., and metamyelocytes 11 per cent.). There was one nucleated red cell for every 200 white cells. The outer manubrial plate was very hard, and no marrow could be aspirated; an iliac crest bone biopsy showed a fairly advanced stage of myelosclerosis (see Plate 17, Fig. 4). Without treatment she has remained free of symptoms for a period of three years, and her blood picture is still very satisfactory (Fig. 2). Gall-stones were found on routine X-ray examination of the abdomen.

2. *Symptomatic group (23 cases).* The majority of patients complained of symptoms that could be attributed to myelosclerosis, as follows:

Symptoms	*Number of cases*
Anaemia: dyspnoea, tiredness	20
Splenomegaly: (1) heavy feeling in the abdomen and fullness after meals	12
(2) pain due to infarcts	2
Bone involvement: deep pain of a 'rheumatic' character, mainly situated around the shoulders and hip-joints, and to a lesser extent over the shafts of the long bones	8
Loss of weight	6
Gout	1
Anginal pain (due to severe anaemia)	2

Example: Case 17. For three months a housewife aged 48 years had complained of lassitude, dyspnoea on exertion, loss of weight, and a feeling of abdominal

distension, especially after meals. The spleen was moderately enlarged, being felt 5 cm. below the costal margin, and the liver was palpable 3 cm. below the costal margin. Blood examination showed a moderate anaemia: haemoglobin 9·0 gm. per 100 ml. (61 per cent.), red cells 3,130,000 per c.mm., and white cells 4,700 per c.mm. The blood film showed several megakaryocytes and many normoblasts; a differential count showed polymorphs 29·5 per cent., lymphocytes 39 per cent., eosinophils 1 per cent., basophils 2 per cent., myeloblasts 1 per

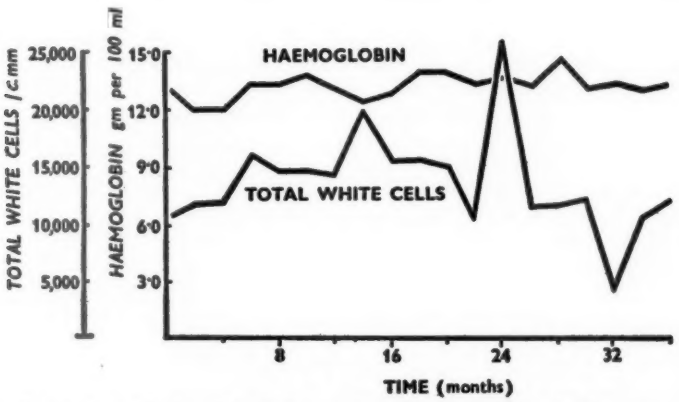

FIG. 2. Case 14. An untreated case of myelosclerosis, showing haemoglobin levels and total white-cell counts over a three-year period.

cent., promyelocytes 1·5 per cent., myelocytes 6·5 per cent., metamyelocytes 11 per cent., monocytes 3·5 per cent., and megakaryocytes 5 per cent.; there were 13 nucleated red cells per 200 white cells. Examination of the sternal marrow showed normal cellularity, and numerous megakaryocytes, most of them having single, round, relatively small nuclei and clusters of platelets attached to them, but some having large bilobed nuclei. The myeloid and erythroid cells were present in their normal percentages. A bone biopsy confirmed myelosclerosis in an early stage (Plate 17, Fig. 3). After transfusions amounting to two pints of packed cells the haemoglobin level rose to 13·1 gm. per 100 ml., and the patient has remained very well, without further anaemia, for six months.

3. '*Hypersplenism*' (*Cases 1 and 23*). Occasionally myelosclerosis may present the features of a haemolytic anaemia, or a haemorrhagic diathesis due to thrombocytopenia. This type of presentation or complication has been labelled 'hypersplenism', but in the presence of an acellular fibrotic marrow such terminology does not seem accurate. It is in this type of case that Green, Conley, Ashburn, and Peters (1953) and Nelson (1954) have reported that splenectomy was at least temporarily beneficial.

Example: Case 1. A man of 52 years was referred to us from another hospital with a history of massive splenomegaly and a progressive leucoerythroblastic anaemia which was refractory to transfusions. He had received 60 pints of blood in the previous six months. Blood examination showed haemoglobin 6·4 gm. per 100 ml., red cells 2,240,000 per c.mm., and white cells 8,050 per c.mm. (polymorphs 55 per cent., lymphocytes 16·5 per cent., eosinophils 2 per

TABLE II

Detailed Blood Findings in 28 Cases of Myelosclerosis when the Diagnosis was First Made

Case number	Haemoglobin (gm./100ml.)	Red cells (millions/c.mm.)	Platelets/c.mm.	White cells/c.mm.	Polymorphs %	Lymphocytes %	Eosinophils %	Basophils %	Monocytes %	Metamyelocytes %	Myelocytes %	Promyelocytes %	Myeloblasts %	Megakaryocytes %	Nucleated red cells per 200 white cells
1	6·4	2·24	72,000	3,050	55·0	16·5	2·0	0	0·5	12·0	12·5	1·0	0·5	0	3
2	9·2	3·19	305,000	5,200	39·0	29·0	1·0	1·0	7·5	10·0	6·0	0	6·5	0	17
3	10·1	3·99	643,000	11,200	32·0	8·5	2·5	3·0	1·0	30·0	10·5	2·5	10·0	0	22
4	9·0	3·07	215,000	10,500	40·5	9·5	0	3·0	17·0	11·5	17·0	0	1·5	0	61
5	4·4	1·48	155,000	4,800	64·0	17·5	0	0·5	6·5	5·0	6·5	0	0	0	30
6	11·2	3·99	684,000	21,000	58·0	10·5	1·5	1·0	1·5	9·5	4·0	2·5	5·5	6·0	16
7	6·5	2·57	50,000	3,400	74·5	17·0	4·0	0	1·5	3·0	0	0	0	0	2
8	7·4	2·99	276,000	7,800	54·0	23·0	5·0	0·5	8·5	3·5	3·5	1·5	0·5	0	26
9	10·8	..	360,000	42,000	60·0	9·0	3·0	7·0	2·0	8·0	4·0	5·0	2·0	0	16
10	9·8	3·61	310,000	3,200	63·5	20·0	0	0	6·0	0	2·5	1·0	1·0	6·0	5
11	8·9	3·8	305,000	7,500	54·0	11·0	3·0	4·0	0·5	4·5	8·0	1·5	13·5	0	6
12	9·8	3·61	128,000	3,200	66·5	20·0	6·0	0	0	3·0	2·5	1·0	1·0	0	5
13	8·3	2·8	393,000	17,950	49·5	9·5	0	13·5	4·0	7·5	11·5	1·5	1·5	1·5	3
14	12·4	4·13	210,000	11,100	63·0	14·0	0·5	0·5	3·0	11·0	4·5	2·0	1·5	0	1
15	11·5	4·3	240,000	7,600	48·5	26·0	0·5	1·0	4·0	7·0	11·0	1·0	1·0	0	14
16	6·2	2·0	200,000	5,400	60·0	18·0	2·0	0	2·0	10·0	4·0	0	4·0	0	20
17	9·0	3·13	284,000	4,700	29·5	39·0	1·0	2·0	3·5	11·0	6·5	1·5	1·0	5·0	13
18	19·9	6·4	64,000	23,000	57·0	12·5	0·5	1·0	18·0	3·0	7·0	0·5	0·5	0	12
19	9·7	4·7	190,000	34,600	56·5	7·0	0	0	25·5	6·0	3·5	0	1·5	0	9
20	8·9	2·8	180,000	7,400	63·0	29·0	2·0	1·0	4·0	0	1·0	0	0	0	28
21	8·9	5·02	110,000	32,000	66·0	7·5	1·0	0	0·5	11·5	13·0	0	0·5	0	7
22	8·6	3·41	325,000	5,300	66·5	17·5	2·5	3·0	1·5	6·0	1·5	0·5	1·0	0	5
23	9·7	2·95	34,000	5,100	30·5	48·0	0	0·5	5·0	5·0	6·5	0	4·5	0	39
24	5·0	1·6	140,000	6,650	76·0	11·5	1·5	0	4·0	4·5	1·5	0	1·0	0	6
25	4·7	1·7	281,000	3,200	64·5	15·5	0	0	3·5	7·0	5·0	0	1·5	3·0	20
26	9·5	3·9	230,000	6,200	70·0	18·0	2·0	2·0	2·0	3·0	1·0	2·0	0	0	4
27	13·6	5·6	690,000	17,650	46·5	12·5	2·0	6·5	3·5	10·5	2·5	1·0	15·0	0	1
28	8·9	3·4	183,000	13,000	44·5	23·0	0·5	0·5	7·5	15·0	4·5	2·5	1·5	0·5	6

cent., monocytes 0·5 per cent., metamyelocytes 12 per cent., myelocytes 12·5 per cent., promyelocytes 1 per cent., and myeloblasts 0·5 per cent. There were three nucleated red cells per 200 white cells. Reticulocytes were 3 per cent., and platelets 72,000 per c.mm.; the blood group A, and Rhesus-negative. It was impossible to penetrate the outer manubrial plate, but an iliac crest bone biopsy confirmed myelosclerosis in a fairly advanced stage. In spite of several transfusions the anaemia progressed (haemoglobin 3·8 gm. per 100 ml.) and red-cell survival rates showed that after seven days only 5 per cent. of the transfused cells remained in the peripheral blood.

A splenectomy was performed by Mr. H. T. Simmons. The spleen was free from adhesions, and weighed 1,296 gm. The liver was not enlarged, and a small piece was taken for examination. Sections of both spleen and liver showed marked siderosis and extramedullary haemopoiesis, without loss of anatomical structure. The liver showed a moderate degree of cirrhosis. By the 30th day after operation the haemoglobin level had risen to 10·4 gm. per 100 ml., and was maintained without further transfusions for four months; the patient then had bleeding from the nose and gums, necessitating further transfusions. In spite of transfusions the bleeding from the nose and mouth persisted, ulceration of the fauces developed, and he died of bronchopneumonia seven months after the operation. His last blood count showed only 300 white cells per c.mm., and the platelets remained persistently less than 50,000 per c.mm.

Thus splenectomy had had a temporary beneficial effect on his clinical condition, and the haemoglobin level had remained at a much higher level for four months without transfusion. There was not the expected leucocytosis or thrombocytosis that others have reported after splenectomy in myelosclerosis. After operation the liver progressively increased in size, until at the time of death it occupied most of the abdomen; it showed numerous areas of haemopoiesis and siderotic cirrhosis.

Other clinical findings. The spleen was always easily palpable, and in 22 cases it extended below the umbilicus into the pelvis. At the time of diagnosis the liver was palpably enlarged in 10 cases, and in four more it became palpable later in the disease. The enlargement was only slight, extending about 2 to 6 cm. below the costal margin, except in Case 1, in which after splenectomy the liver attained a considerable size. Ascites developed as a late complication in two cases (Nos. 3 and 16), and was associated with gross splenomegaly and moderate enlargement of the liver with a hard edge. The cause of death in every instance was progressive anaemia, which blood transfusions no longer affected.

Blood Findings (Table II)

The majority of patients had a moderate degree of anaemia, which was normochromic, except in three cases in which it was moderately hypochromic (mean corpuscular haemoglobin concentration 27 to 30 per cent.). The platelet counts varied considerably, and were within normal limits in over half the cases. Marked thrombocytopenia developed terminally in eight cases, and was associated with a severe and progressive anaemia. The total white-cell counts never reached the level which characterizes chronic myeloid leukaemia, and in all cases were persistently less than 50,000 per c.mm., in only three exceeding 25,000 per c.mm. The moderately raised or normal white-cell count in the presence of considerable splenomegaly was usually the first indication of the true nature of

the disease. All cases showed normoblasts in the blood film at some stage, and in many cases they were numerous, for example, 61 normoblasts per 200 white cells in Case 4. The normoblasts were morphologically normal, and of the intermediate and late types. They were not constantly present throughout the whole course of the disease, and their absence in an isolated blood film in no way excludes the diagnosis. Stippled red cells, anisocytosis, and poikilocytosis were present when there was appreciable anaemia, and were roughly proportional to its severity. Megakaryocytes were seen in blood films from the start in six cases, and appeared in small numbers at some stage in two more. Myeloblasts were seen in many cases (for example, Case 27), and commonly persisted throughout a long clinical course without deterioration in the clinical condition.

X-ray Changes in the Bones

The incidence of X-ray changes in the bones in myelosclerosis reported by different observers has varied from one-third to one-half of the cases. The characteristic changes are said to occur in the medulla, and the cortex is not involved. Hickling (1937), Vaughan and Harrison (1939), Rosenthal and Erf (1943), Sussman (1947), and Nelson (1954) described the changes as consisting of disorganization of the trabecular pattern, with deposition of bone throughout the marrow from focal areas of osteosclerosis. The changes may affect any bone, with the exception of the skull bones, which are completely immune. The skull is invariably involved in Albers-Schönberg disease, in both the dominant and recessive varieties. The Mendelian recessive type may not be found until much later in life, as reported by Bonta (1928) in a patient of 58 years, and by McPeak (1936) in a patient of 76 years. The skull X-ray permits its differentiation from idiopathic myelosclerosis. In Nelson's experience the presence of bone pain in myelosclerosis can be correlated with the rapidity of progression of the medullary lesion, and these phenomena may be accelerated by splenectomy. We have observed the same correlation, and eight out of nine patients who showed X-ray changes complained of pains around the affected bones. The following bones showed a characteristic radiographic picture: humerus (five cases), lumbar vertebrae (two), femur (two), and tibia (one case). The diffuse mottling of the bones (Plate 18) is shown in the ribs and humerus (Fig. 6) and lumbar vertebrae (Fig. 7). These changes were found at all stages in the evolution of myelosclerosis as judged by the bone biopsies; they occurred at an early stage in Case 17, and were absent in the late stages in three cases (Nos. 4, 16, and 20). Considerable difficulties were experienced in the interpretation of the skeletal radiographs; bones which on first examination appeared abnormally dense showed a normal pattern on re-examination with different exposures. The normal variation, taking into account age, sex, and physique, in skeletal X-rays which were used for controls, was so considerable that many deviations were reconsidered and thought to be normal. In our experience skeletal radiographs were not very informative, and were the least useful of all the diagnostic procedures carried out in the investigation of myelosclerosis.

TABLE III

Myelograms in 15 Cases of Myelosclerosis

(*Figures in percentages*)

Case number	*Cellularity*	*Polymorphs*	*Metamyelocytes*	*Myelocytes*	*Promyelocytes*	*Myeloblasts*	*Eosinophils*	*Basophils*	*Proerythroblasts*	*Early normoblasts*	*Intermediate normoblasts*	*Late normoblasts*	*Megakaryocytes*	*Monocytes*	*Plasma cells*	*Lymphocytes*
3	H	28·2	4·6	4·0	0·6	3·4	1·6	0·7	0	0·8	5·5	42·0	0	0·8	0	7·8
4	H	20·4	12·8	8·2	1·4	2·6	0	0	0	0·2	1·4	32·0	0·6	3·6	0	16·8
7	H	28·0	4·4	0·4	0	0·2	1·0	0·6	0·8	0·8	3·8	50·4	0	1·0	0	8·6
8	H	37·0	10·8	13·2	4·0	2·0	0·6	0	0	0·4	1·6	4·6	0	2·2	0	23·6
13	H	20·0	10·5	7·5	1·5	0·5	0·5	0·5	0	0	0·5	21·5	0	9·0	0·5	27·5
15	H	20·0	6·4	4·8	1·8	3·0	0	2·0	0·6	1·6	3·2	49·0	1·8	0·6	0·4	4·8
16	H	13·8	8·2	2·6	0·2	1·0	3·0	0·8	0	0·4	0·6	8·0	0	7·2	0	54·2
17	N	24·0	13·6	3·0	1·0	3·4	2·0	1·4	0·2	0·2	0·8	13·6	8·0	2·0	0	26·8
19	H	31·0	18·0	8·8	3·4	3·6	0·2	0	0	0·2	0·8	8·4	0·2	15·8	0·4	9·2
20	H	29·6	7·4	1·6	0·4	1·4	0·8	0·2	0	0	0	20·2	0·2	16·8	0	21·4
21	N	62·2	12·2	6·6	1·0	0·6	3·0	2·0	0	0·2	0·2	5·2	0	1·4	0	5·2
22	H	24·8	2·8	2·8	0·6	0·2	0·4	0·4	0	3·4	5·4	41·8	0·4	4·0	0·6	11·4
24	N	41·4	15·0	4·4	1·6	1·4	1·0	0·2	0	0·4	2·0	18·6	0·2	3·6	0	10·2
25	H	41·0	4·5	2·5	0	0·5	2·0	0	0	0	5·5	6·5	0	5·0	0	32·5
26	H	59·0	18·0	5·6	4·0	0·6	0·6	2·2	0	0	0·2	0·8	0	1·4	0	7·6

In 13 cases (Nos. 1, 2, 5, 6, 9, 10, 11, 12, 14, 18, 23, 27, and 28) no marrow was aspirated.
H = Hypoplastic (12 cases). N = Normal cellularity (3 cases).

Marrow Findings (Table III)

In 13 patients it was impossible to penetrate the outer manubrial plate; in 12 the needle was inserted only after considerable difficulty, and a small volume of very hypoplastic marrow was aspirated; the cellularity in the remaining three cases was considered normal. Marrow punctures were attempted in the manubrium and the body of the sternum, and in the iliac crest, before concluding that aspiration was impossible. The typical picture was one of greatly reduced cellularity, with very occasional groups of megakaryocytes, polymorphs, and normoblasts. It is noteworthy that in eight of the 12 very hypoplastic marrows the normoblasts in differential counts were considerably increased in number, indicating an attempt of the remaining haemopoietic tissue to compensate for the anaemia produced by marrow fibrosis. Most of the granulocytes were polymorphs and metamyelocytes, and the immaturity of the myeloid series seen in chronic myeloid leukaemia was not present in any myelosclerotic marrow. In myeloid leukaemia, whatever the level of the white-cell count, the marrow is easily obtained, and is hyperplastic, with many myelocytes and promyelocytes. In Case 22 five attempts at marrow puncture were made before a small volume of marrow was aspirated; it was markedly hypoplastic, and late normoblasts comprised 41·8 per cent. of the total cells. This is evidence in favour of the patchy distribution of myelosclerosis, and again illustrates the compensatory erythropoiesis of the remaining active marrow The most important single diagnostic procedure in the investigation is to obtain, before any treatment is given, a fair-sized wedge of bone for histological examination. In all our cases a wedge of bone was removed from the iliac crest under a general anaesthetic. The histological picture was found to vary somewhat according to the stage of the disease, and can be conveniently described in three stages.

Early stage (Plate 17, Fig. 3). The marrow spaces in parts of the section are occupied by varying amounts of cellular fibrous tissue, containing many dilated capillaries and very often numerous large megakaryocytes with one, two, or more nuclei; these cells are often located near the capillary walls. Many of the megakaryocytic nuclei have a reticular chromatin pattern. In other parts of the section the marrow spaces are filled with normal haemopoietic marrow. There is no thickening of bone trabeculae, and osteoid seams are of normal thickness.

Intermediate stage (Plate 17, Fig. 4). The marrow spaces are nearly all filled with fibrous tissue, and there is little haemopoietic marrow. Megakaryocytes are present, but not usually as plentiful as in the early stage. The bony trabeculae appear broader than normal, and are increased in number and complexity.

Late stage (Plate 17, Fig. 5). The bony trabeculae are very broad, and osteoid seams are abnormally thick. The marrow spaces, many of which are greatly reduced in size, are filled with an acellular fibrotic tissue, there is virtually no haemopoietic marrow, and megakaryocytes are very scanty or absent.

In the early stages the cellularity is in no way comparable to the homogeneously increased cellularity that is seen in chronic myeloid leukaemia and

TABLE IV

Splenograms in 13 Cases of Myelosclerosis

(Figures in percentage)

Case number	Myeloid series								Normoblastic series				Other cells					
	Polymorphs	Metamyelocytes	Myelocytes	Promyelocytes	Myeloblasts	Eosinophils	Basophils	Total	Proerythroblasts	Early normoblasts	Intermediate normoblasts	Late normoblasts	Total	Lymphocytes	Plasma cells	Monocytes	Reticulum cells	Megakaryocytes
1	16·0	2·0	8·5	0	2·0	1·0	0	29·5	1·5	4·0	18·5	18·5	42·5	22·0	2·0	1·0	2·0	1·0
2	18·0	9·5	6·5	1·0	1·0	1·0	0·5	37·5	0	3·0	13·5	17·0	33·5	26·0	1·5	1·0	0	0·5
3	18·4	8·8	3·2	0	0	0	0	30·4	0	0	16·4	32·0	48·4	20·4	0	0·6	0	0·2
4	17·0	3·0	3·0	0	0	2·5	0	25·5	0	0·5	20·0	17·0	37·5	36·0	0·5	0	0·5	0
5	14·8	6·0	1·6	0·8	0	0·4	0	23·6	1·6	4·0	12·2	21·2	39·0	33·2	1·0	1·6	1·6	0
6	17·0	5·0	2·0	1·0	0	0	0	25·0	1·0	3·0	17·0	14·0	35·0	34·0	2·0	2·0	1·0	1·0
7	18·4	5·2	1·6	0	0·8	2·0	0·8	28·8	0·8	2·0	21·2	14·0	38·0	31·6	0·4	0·8	0·4	0
12	14·5	14·0	2·0	0	0	2·5	0·5	33·5	0	1·0	15·0	17·5	33·5	28·0	1·5	2·0	1·5	0
13	11·8	4·8	2·4	0	0·2	0·2	1·4	20·8	0	0	17·8	36·0	53·8	23·6	0·4	1·4	0	0
16	25·0	0	6·0	0	0	0	0	31·0	0	2·0	11·0	8·6	21·6	44·0	0	3·0	0	0·4
17	13·6	2·8	0·6	0	0·2	3·0	0·2	20·4	0·6	4·0	24·6	23·4	52·6	19·0	0	2·4	1·6	4·0
22	28·0	8·2	1·0	0	0	0·8	0·2	38·2	0	1·0	16·8	19·0	36·8	22·0	0	0·6	0·6	1·8
24	9·8	4·0	2·2	0·8	0	0	0	16·8	0	3·2	7·2	12·8	23·2	49·8	2·2	5·6	1·6	0·8

polycythaemia vera. Although three stages have been described in the evolution of the fully established case of myelosclerosis, all stages may be seen in any one section, and only a preponderance of one stage gives the clue to the actual severity of a particular case. A similar histological picture is seen in some sections of metastatic carcinoma involving bones, and a careful search for tumour cells is always necessary; they are found interspersed in the fibrous matrix; Custer (1949) shows some beautiful photomicrographs illustrating this point.

Splenic Puncture (Table IV)

Splenic puncture was performed in 13 patients, and counts of 1,000 cells were made; the results are shown in Table IV. The puncture was made through the anterior abdominal wall just below the costal margin, and a few drops of splenic fluid were aspirated into the needle. There were no troublesome sequels. Splenograms in myelosclerosis have very rarely been reported, and Moeschlin (1951) urged investigators to publish details of such cases. He considered that it ought to be possible to distinguish between osteosclerosis due to leukaemia and osteosclerosis in which splenomegaly is due to compensatory myeloid metaplasia. In leukaemic osteosclerosis the splenic punctures showed only 10 to 25 per cent. lymphocytes, which he interpreted as indicating a complete loss of splenic architecture, whereas in primary osteosclerosis the lymphocytes were relatively numerous (50 to 60 per cent.) indicating a greater preservation of the histological structure in the non-leukaemic cases. In the present investigation the lymphocytes varied from 20·4 per cent. to 49·8 per cent., the erythroblasts from 21·6 per cent. to 53·8 per cent. (over 30 per cent. in 11 cases), and the total myeloid cells from 16·8 per cent. to 38·2 per cent., the myelocytes never exceeding 8·5 per cent. Most of the myeloid cells were normal mature polymorphs and metamyelocytes, and none of the immature granulocytes showed the disturbance of development in the nuclei and cytoplasm which is seen in chronic myeloid leukaemia. The pattern described, consisting of a moderate to considerable increase in normoblasts, the presence of considerable numbers of megakaryocytes, a moderate increase in myeloid cells with few cells more primitive than the metamyelocytes, and lymphocytes about 20 to 50 per cent., is an entirely different picture from those seen in chronic myeloid leukaemia and in polycythaemia vera, and shows very clearly the extramedullary haemopoiesis taking place in the spleen. In splenograms of chronic myeloid leukaemia very few lymphocytes were found (less than 10 per cent.), and practically all the cells were of the myeloid series, with many myelocytes, many of which were abnormal, promyelocytes, and some myeloblasts. In polycythaemia vera the cells are mostly polymorphs and lymphocytes, normoblasts being very few. Our findings indicate a greater preservation of the splenic architecture in myelosclerosis than in chronic myeloid leukaemia, but figures for total normoblasts were considerably higher than those reported by Moeschlin (1951).

Discussion

Provided the diagnosis is verified histologically by bone biopsy before any

treatment is given, there is no difficulty in distinguishing myelosclerosis from chronic myeloid leukaemia and polycythaemia vera. Several cases of myelosclerosis have been reported complicating polycythaemia vera and chronic myeloid leukaemia after treatment by irradiation, but X-rays are known to be an aetiological factor in the production of myelosclerosis. It is still uncertain whether myelosclerosis develops in the natural course of these conditions; among 197 cases of chronic myeloid leukaemia and 90 cases of polycythaemia vera studied in this clinic, so far only two patients with polycythaemia have developed myelosclerosis, and both had received whole-body irradiation. The treatment of leukaemia and polycythaemia by irradiation, or by some drugs, causes destruction of the marrow cells, and fibrosis may well be expected in patients who survive for long periods. Recent histochemical work has suggested that examination of the alkaline phosphatase in the leucocytes may help in diagnosis. Valentine, Beck, Follette, Mills, and Lawrence (1952) reported that in polycythaemia vera and in chronic myeloid leukaemia consistent changes were found in the alkaline phosphatase and glycogen contents of leucocytes. In polycythaemia vera both alkaline phosphatase and glycogen were increased, even when the white-cell count was over 50,000 per c.mm., while in chronic myeloid leukaemia the alkaline phosphatase in the leucocytes was much diminished. These changes were remarkably uniform, were found in both early and late stages of the diseases, and were uninfluenced by treatment. In a group of 'atypical myeloproliferative disorders' a variety of changes was found, suggesting that the group had a heterogeneous aetiology. Moloney and Lange (1954) described four cases of 'pre-clinical' myelogenous leukaemia developing in atomic-bomb survivors, and found that very low alkaline phosphatase values in the leucocytes preceded any definite cytological evidence of leukaemia in the blood and marrow. Our results were strictly in accord with those of Valentine, Beck, Follette, Mills, and Lawrence, both in polycythaemia vera and in chronic myeloid leukaemia; in 19 cases of myelosclerosis that we have investigated the leucocyte alkaline phosphatase was found to be very variable, being normal in 10 and diminished in seven cases; it was increased in the two patients with polycythaemia vera in whom myelosclerosis developed after irradiation therapy.

We do not think that the evidence now available supports Dameshek's (1951) theory that polycythaemia vera, chronic myeloid leukaemia, and myelosclerosis are closely related disorders of proliferative activity of the bone-marrow cells. The remarkably constant but very different biochemical patterns in chronic myeloid leukaemia and polycythaemia vera, at all stages in the disease, suggest a fundamental biochemical abnormality characteristic of the particular disease, and if 'transition' forms of these diseases occurred at all commonly these constant patterns would not be expected. In myelosclerosis the lack of a uniform biochemical pattern suggests that myelosclerosis is a morphological entity without aetiological unity, as Wyatt and Sommers (1950) suggested. The previous conception of myelosclerosis is more consistent with our findings; that is, myelosclerosis, with consequent marrow failure, causes blood formation to reappear in the spleen and the liver, and, because these

organs lack the regulatory mechanism possessed by the bone-marrow, cells which are normally confined to the marrow escape into the peripheral blood. The considerable increase in normoblasts found in the splenograms clearly indicates the spleen's compensatory function, and post-mortem examination of the spleen showed widespread erythropoiesis in six cases.

The more favourable results of splenectomy in myelosclerosis reported by Green, Conley, Ashburn, and Peters (1953) are at first sight against the conception of the importance of the spleen participating in extramedullary haemopoiesis; 15 of 29 patients survived for longer than two years, and eight for four years. The removal of a large source of blood formation might be expected to have a rapidly fatal outcome. In Nelson's (1954) detailed report of one case of myelosclerosis, splenectomy was followed by a progressive increase in the size of the liver, until it occupied almost the entire abdomen, and *post mortem* widespread erythropoietic foci were seen scattered throughout the liver. Asher (1955) also reported considerable enlargement of the liver, to 10 inches below the xiphisternum, in a similar case, and in Case 1 of our series it progressively increased in size after splenectomy; four months after the operation, when we last saw the patient, the liver was felt eight inches below the costal margin. We have never seen such a considerable degree of hepatomegaly in any case of myelosclerosis in which splenectomy had not been performed. Though the spleen usually serves a useful compensatory function, occasionally, for unknown reasons, it may start destroying red cells and platelets. It is only in this type of case that splenectomy should be considered. The outcome after splenectomy may well depend upon the capacity of the liver to take over this extra burden of blood formation, and this function no doubt accounts for the considerable hepatomegaly described in the above three cases.

Our findings show that myelosclerosis may not affect all parts of the bone-marrow to the same extent simultaneously, and that parts of the marrow least affected take part in the compensatory erythropoietic hyperplasia; the high percentage of normoblasts in several of the myelograms supports this conclusion. Many such cases have been described as 'erythroleukaemias', a view which we do not accept. We consider that erythroleukaemia should not be diagnosed unless there are erythroblasts in the peripheral blood and a hyperplastic marrow which is easily obtained, containing many erythroblasts, some of which are abnormal, having one, two, or more nuclei with the chromatin network frequently arranged like the megaloblasts—that is, megaloblastiform cells. This type of cell has been described and illustrated by Martin and Bayrd (1954) and Israëls (1955). Bone biopsies in cases of erythroleukaemia which we have studied all showed a picture very different from that of myelosclerosis: cellularity was considerably increased, and the cells were almost all erythroblasts, many of which were abnormal; there was no evidence of myelosclerosis.

A study of myelosclerosis reveals the remarkable compensatory functions possessed by the body in the presence of a widespread and extensive pathological process. As a result, the patient may remain almost or completely free of symptoms for many years and maintain a fairly constant haemoglobin level.

The beneficial effects of any form of treatment in myelosclerosis are extremely difficult to assess, and we believe that all treatment, including blood transfusions, should be withheld until there is definite clinical and haematological deterioration. Cirrhosis of the liver may develop in myelosclerosis when no transfusions have been given, but is more commonly seen in those who have received many blood transfusions. Two of our patients were found either at autopsy or at operation to have a marked degree of cirrhosis; one patient had received transfusions totalling 60 pints of blood; the other patient had had no transfusions, but had developed serious ascites requiring frequent paracenteses; in each case there was deposition of considerable amounts of iron in the liver, spleen, and marrow. Wyatt and Sommers (1950) also reported the development of cirrhosis in myelosclerosis. The deposition of haemoglobin iron after transfusions may well initiate or accelerate fibrosis in the liver, and possibly also in the bone-marrow. Consequently we prefer to withhold transfusions, even in the presence of a moderate degree of anaemia (say nine gm. or more per 100 ml.), until there is a definite and progressive fall in the haemoglobin level and clinical symptoms have appeared. If the number of transfusions required to maintain a reasonable haemoglobin level is excessive and unmanageable, then splenectomy seems advisable. Green, Conley, Ashburn, and Peters (1953) considered that a haemorrhagic diathesis due to thrombocytopenia and haemolytic anaemia was the outstanding indication for splenectomy, and their excellent results appear to confirm this view. Splenectomy has no other beneficial effect on the course of the disease, and may have deleterious effects, as described by Nelson (1954), with an increase in bone pain associated with progressive radiological changes in the bones.

We consider that the name myelosclerosis should be reserved for the disorder which presents the following features: there is anaemia, which eventually becomes progressively worse, with a leucoerythroblastic peripheral blood count; sometimes megakaryocytes may be present. It is difficult or impossible to aspirate samples from the bone-marrow; if any marrow is obtained, it shows a hypoplastic state and megakaryocytes are present, but sometimes it is normal, or even patches of erythroblastic activity may be found. Splenomegaly is a constant and prominent feature, and splenic punctures show considerable normoblastic activity and increased numbers of granulocytes, while megakaryocytes are constantly present. Certain diagnosis necessitates a bone biopsy from a marrow-containing site such as the iliac crest, and biopsy should demonstrate one of the three stages of fibrosis and sclerosis described above, often with persistence of megakaryocytes. Radiological examination of the bones sometimes shows abnormalities, but they are neither consistent nor typical.

Treatment is mainly by means of blood transfusions, which should not be begun until the lowered haemoglobin level is causing clinical disability, and then a level of more than nine gm. per 100 ml. should be maintained. Splenectomy is a desperate measure, to be adopted when the spleen develops haemolytic activity; the extramedullary haemopoietic activity is taken over by the liver, and thereby life may be prolonged for a time.

We wish to thank Professor A. C. P. Campbell and Dr. J. Ball, of the Department of Pathology, Manchester University, for their valuable assistance in the interpretation of the pathology of the bone biopsies; Dr. E. Gray and Mr. D. Lloyd-Griffiths, of Manchester Royal Infirmary, for their valued advice in the interpretation of the skeletal radiographs; and the Department of Medical Illustration, Manchester Royal Infirmary, for photographing Figures 1, 2, 6, and 7.

Summary

1. Twenty-eight cases of myelosclerosis have been investigated by skeletal radiographs, blood and marrow examination, splenic punctures, and iliac crest bone biopsies.

2. The most important single diagnostic procedure is the bone biopsy, which should be performed before any treatment is given. The histological picture was found to vary according to the stage in the disease, and can be divided into three stages.

3. The splenograms showed definite evidence of extramedullary haemopoiesis, the pattern being quite different from that seen in chronic myeloid leukaemia and polycythaemia vera.

4. Two patients developed cirrhosis of the liver associated with widespread haemosiderosis.

5. Myelosclerosis, chronic myeloid leukaemia, polycythaemia vera, and erythroleukaemia are clinically and pathologically distinguishable, and not simply different facets of a single disease.

6. The indications for treatment by blood transfusions and splenectomy are discussed.

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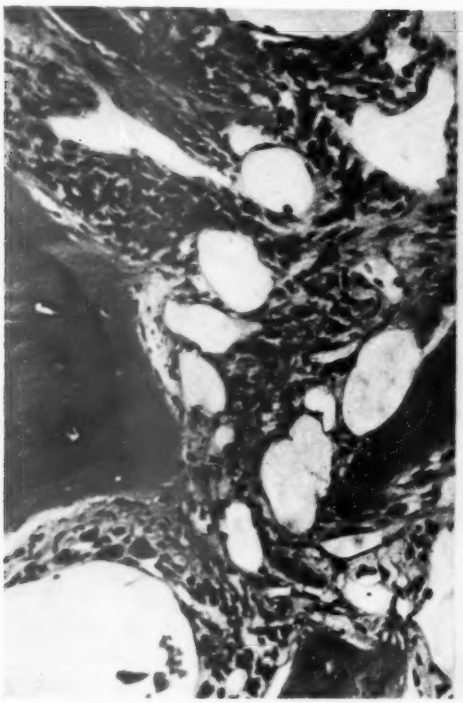

FIG. 3. Case 17. Iliac crest bone biopsy. Early stage of myelosclerosis

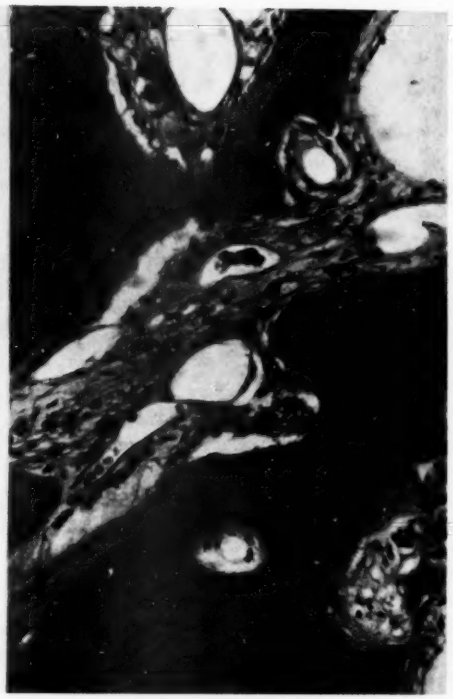

FIG. 4. Case 3. Iliac crest bone biopsy. Intermediate stage of myelosclerosis

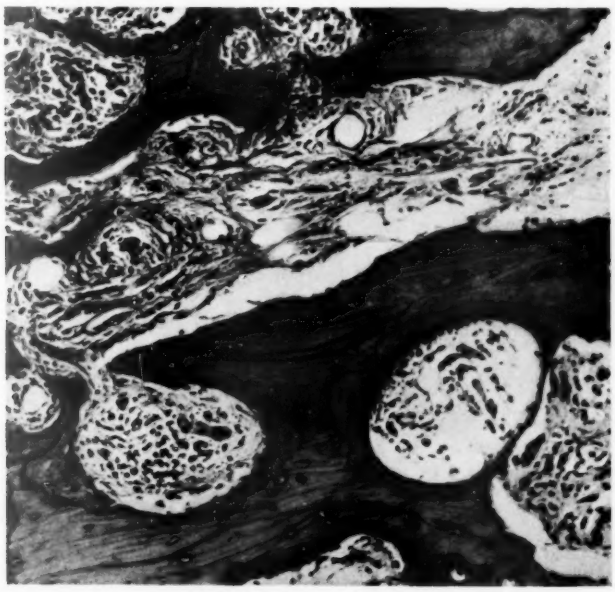

FIG. 5. Case 2. Iliac crest bone biopsy. Advanced stage of myelosclerosis

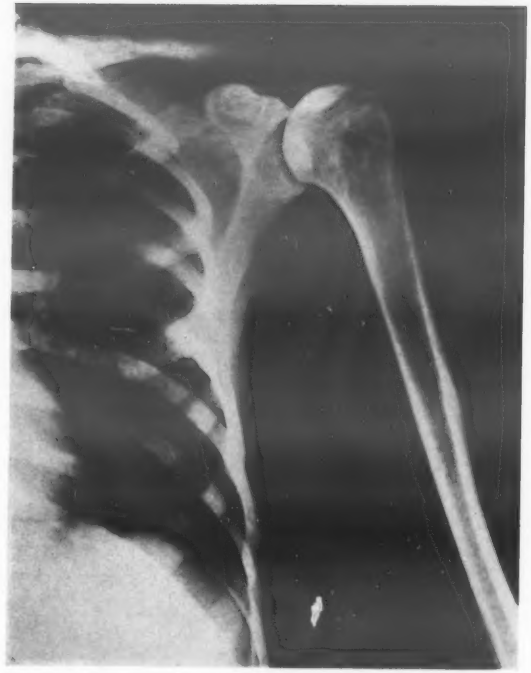

FIG. 6. Case 13. Diffuse mottling of the ribs and upper end of the humerus

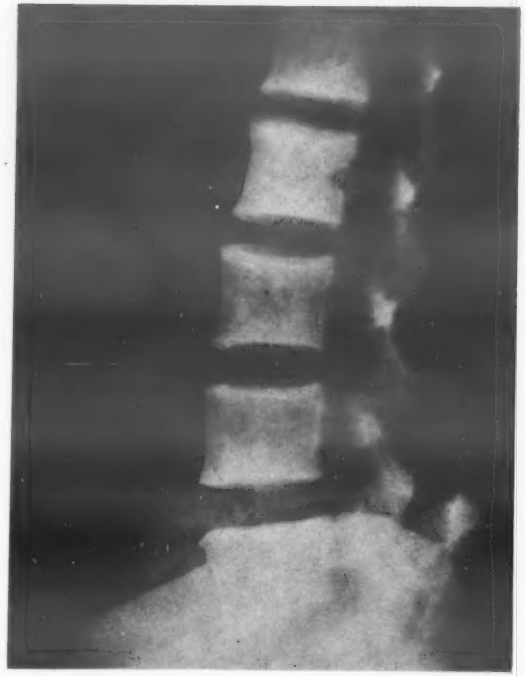

FIG. 7. Case 14. Lateral view of the lumbar spine, to show mottling of the vertebral bodies

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TOTAL ADRENALECTOMY FOR MALIGNANT HYPERTENSION[1]

By W. VAN 'T HOFF

(From the Westminster Hospital, London)

With Plate 19

MALIGNANT hypertension has a grave prognosis. If the presence of papilloedema is taken as the criterion for the diagnosis of the malignant phase of hypertension (Wood, 1950; Pickering, 1952; Fishberg, 1954), nearly 80 per cent. of untreated patients die within a year of diagnosis (Keith, Wagener, and Barker, 1939). Salt restriction, sympathectomy, and the use of ganglion-blocking agents have to some extent improved the outlook. The removal of both adrenal glands has been advocated, and it is important to assess the rationale and results of this form of therapy. Changes in blood-pressure in hyper- and hypoadrenal states in man suggest that the adrenal gland may play a significant role in the maintenance of blood-pressure, and this view is supported by evidence from animal experiments. The development of hypertension in dogs after occlusion of a renal artery is prevented by bilateral adrenalectomy (Goldblatt, 1937). Similarly, in rats with hypertension produced by either renal artery occlusion or total nephrectomy, the removal of both adrenals reduces the blood-pressure to normal or below, unless added salt is given (Floyer, 1951). In man, hypertension in Cushing's syndrome can be relieved by subtotal adrenalectomy (Priestley, Sprague, Walters, and Salassa, 1951), and Addison's disease is often associated with a low blood-pressure. Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt (1952) have described two hypertensive patients whose blood-pressure fell to normal when they developed adrenal insufficiency. When deoxycorticosterone acetate was given the hypertension returned, but when cortisone with only a minimal quantity of deoxycorticosterone was administered the blood-pressure fell to normal again. Although there is no good evidence that adrenocortical hormones play an initiating role in essential hypertension, there is no doubt that they play a part in the maintenance of normal, and probably also of raised, blood-pressure. Treatment of essential hypertension by partial adrenalectomy was first reported in 1934 by DeCourcy, who believed that the resulting improvement in eight patients was due to removal of the adrenal medulla. In 1950 he reported a total of 30 patients from whom he had removed four-fifths of each adrenal gland, with a significant reduction in blood-pressure. Since then several other series have been reported (Bowers, 1954; Jeffers, Zintel, Hills, Hafkenschiel, Langfeld, Sellers, and Wolferth, 1954; Revell,

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Borges, Yeager, Arnold, and Ahlquist, 1954). The advent of satisfactory replacement therapy has made possible the complete removal of both adrenal glands, and 40 of the 125 patients described by Jeffers and his colleagues underwent total adrenalectomy; in nearly all, however, the operation was combined with some form of sympathectomy, which makes it difficult to assess the value of adrenalectomy alone in this group of cases. Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt (1952), however, and more recently Arnott (1956), have given well documented accounts of the results of hypertension treated only by total adrenalectomy; these cases will be discussed later.

Cases Studied

The effect of adrenalectomy has been studied in five patients with malignant hypertension and good renal function. All were men, aged from 26 to 57 years, and before operation all had a mean resting diastolic blood-pressure of 130 mm. Hg or more, except one patient (Case 5) whose diastolic pressure was 120 mm. Hg. Four patients (Cases 1, 2, 4, and 5) presented blurring of vision, and all five had papilloedema, retinal haemorrhages, and exudates. One patient (Case 3) was admitted to hospital with haematuria. None gave a history of angina pectoris, or showed any evidence of left ventricular or congestive heart failure. All were able to concentrate urine to a specific gravity of 1,020 or more, and to dilute it to 1,005 or less; in none did the urine contain more than 10 mg. of protein per 100 ml., or any cells. In all patients the blood-urea was below 40 mg. per 100 ml. Intravenous pyelography showed nothing abnormal, except in one patient (Case 3) who had haematuria. In this patient the right kidney appeared smaller than the left, and was found on aortography to have a decreased blood-supply; at autopsy it showed changes due to chronic pyelonephritis.

Patient No. 1 had had a transient external rectus palsy two years before operation, at which time his blood-pressure was 140/85. A month before operation he had an epileptiform fit, and a week later a subarachnoid haemorrhage. Patient No. 2 had previously been well, but the third patient also had had an external rectus palsy three years before operation. At that time his blood-pressure was raised to 200/140, and he was treated with hexamethonium for six months. He was the only one of the five patients who had had any previous specific treatment for raised blood-pressure. He was admitted to the ward two months before operation because of haematuria, and the only fundal changes then were irregular narrowing of the arteries. While in the ward he developed gross bilateral papilloedema and haemorrhages during a period of six weeks (Plate 19, Fig. 4*a*). Patient No. 4 was known to have had a blood-pressure of 160/100 mm. Hg. 17 years, and of 260/150 two years, before adrenalectomy. An episode of confusion and dysphasia occurred three months before operation. Patient No. 5 had had an epileptiform fit a month before operation. All the patients had headaches, which were severe in Cases 3 and 4, and mild in the others, except in Case 1 at the time of the patient's subarachnoid haemorrhage.

TABLE I

Data of Five Cases of Malignant Hypertension treated by Total Adrenalectomy

The blood-pressure figures before operation are the mean of 20 readings; those after operation are single out-patient recordings

Case number	*Sex*	*Age (years)*		*Blood-pressure (mm. Hg)*	*Ocular changes*					*Spinal-fluid pressure (mm. H_2O)*	*Albuminuria*	*Blood-urea (mg./100 ml.)*	*Serum-sodium (mEq./l.)*	*Serum-potassium (mEq./l.)*	*Serum-chloride (mEq./l.)*
					Papilloedema	*Haemorrhages*	*Exudates*	*Visual acuity* R.	*Visual acuity* L.						
1	M	33	Before operation	220/140	+	+	+	6/18	6/12	300	trace	28	136	3·7	95
			6 months after operation	200/140	+	0	0	6/9	6/9	..	trace	..	144	4·5	103
			12 months after operation	220/140	0	0	0	6/6	6/6	250	trace	31	134	4·8	95
			18 months after operation	200/160	0	0	0	6/9	6/9	270	trace	26	132	3·8	92
2	M	48	Before operation	205/145	+	+	+	6/9	6/18	300	trace	36	143	3·8	110
			6 months after operation	200/140	+	+	0	6/9	6/18	..	trace	48	136	4·3	97
3	M	26	Before operation	215/155	+	+	+	..	..	230	trace	17	135	3·4	95
			6 months after operation	240/180	+	0	+	6/5	6/5	..	trace	33	131	4·1	90
			12 months after operation	220/140	0	0	+	6/6	6/6	..	trace	39	136	4·7	105
			18 months after operation	180/130	0	0	0	6/6	6/6	..	trace	66	126	4·0	90
4	M	54	Before operation	200/130	+	+	+	6/12	6/18	300	trace	39	139	4·1	93
			6 months after operation	200/140	+	0	0	6/12	6/18	..	0	50	140	5·5	100
			12 months after operation	190/130	0	0	0	6/9	6/9	260	trace	29	142	4·3	104
			18 months after operation	200/120	0	0	0	6/6	6/6	240	0	41	137	5·0	95
5	M	57	Before operation	175/120	+	+	+	6/9	6/9	160	0	26	137	3·7	100
			6 months after operation	210/140	+	0	0	6/9	6/9	..	0	38	142	4·0	95
			12 months after operation	210/150	0	0	0	6/9	6/9	..	trace	50	133	4·7	97

Bilateral adrenalectomy was carried out through the posterior approach in two stages, except in Case 1, in which a one-stage operation was performed. No difficulties were encountered, except for the occurrence of temporary hypotension in three patients (Cases 1, 2, and 4), necessitating a noradrenalin infusion. Intramuscular cortisone was started two days before operation, in doses of 100 mg. daily before the first operation and 150 mg. daily before the second.

TABLE II

Deaths

Case number	*Died months after operation*	*Cause of death*	*Histological appearance of kidneys*	
			At operation	*Post mortem*
1	19	Pontine haemorrhage	Hypertensive arteriolosclerosis	Hypertensive arteriolosclerosis. Superadded subcapsular fibrosis and arterial thrombosis
2	10	Pontine haemorrhage	..	Hypertensive arteriolosclerosis
3	19	Ruptured dissection of aorta	*Left*: Hypertensive arteriolosclerosis *Right*: ..	Hypertensive arteriolosclerosis Compensatory hypertrophy Diffuse chronic pyelonephritis and old arterial thrombosis
5	12	Cerebral haemorrhage	Hypertensive arteriolosclerosis	Hypertensive arteriolosclerosis

Two hundred mg. and 300 mg. were given on the days of the first and second operations respectively. The dose of cortisone was then gradually reduced to a maintenance level within 12 days. One patient (Case 1) was maintained on 37·5 mg. of cortisone by mouth daily for 14 months, when it was increased to 50 mg. daily because of persistent nausea and weakness for three weeks. The other patients were maintained on 50 mg. daily from the onset; in Case 2 this dose had to be increased to 75 mg. after five months, again because of weakness. All the patients were allowed a normal diet without salt restriction.

Results

After adrenalectomy all the patients felt better; their headaches improved, and they were all allowed to return to work in four months. Papilloedema, haemorrhages, and exudates improved in all cases (Plate 19, Fig. 4*b*). In no patient, however, was there any significant change in blood-pressure as a result of the operation (Table I), and one (Case 3) again entered the malignant phase seven months after operation, with recurrence of headaches and papilloedema, and a further rise in blood-pressure. In view of this poor outcome it was decided to study the effect of altering the maintenance régime by lowering (*a*) the dose of cortisone and (*b*) the salt intake. Patient No. 3 was then readmitted, having entered the malignant phase again during the preceding three weeks. Keeping the dietary sodium intake constant, cortisone was reduced from a maintenance level of 50 mg. daily to 37·5 mg. daily (Fig. 1). After three days he began complaining of weakness and nausea, and these symptoms became worse during the next two days, although he did not actually vomit. The blood-urea rose from 33 mg. to 83 mg. per 100 ml., but there was no significant change in the blood-pressure, nor in the serum-sodium level. In view of the

increasing blood-urea it was considered that, far from improving him, the reduction of cortisone was having an adverse effect, and extra cortisone was therefore given. Hexamethonium, and later pentolinium, were then given, as it

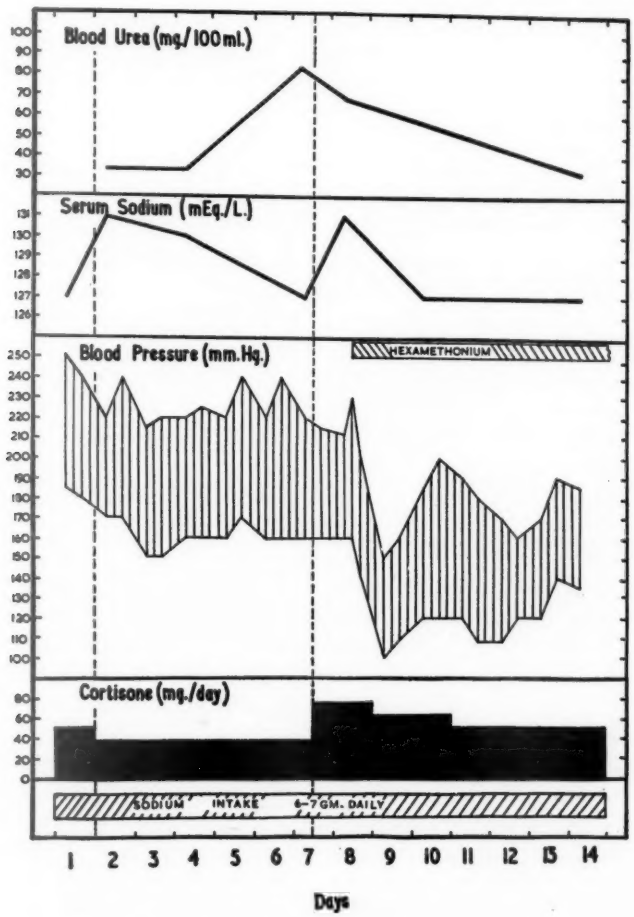

FIG. 1. Effect of reducing the dose of cortisone in Case 3.

was not thought reasonable to withhold such treatment any longer. To study the effect of reducing sodium intake, patient No. 4 was admitted 21 months after operation. The daily dose of cortisone was kept constant at 50 mg., and after a preliminary control period on his normal diet, which contained 300 mEq. of sodium, the sodium intake was reduced to 43 mEq. daily (Fig. 2). The following day he complained of slight nausea, accompanied by weakness. On the fourth day he vomited once, and on the fifth day three times. Only at this stage, when his general condition was deteriorating, did his blood-pressure fall.

His blood-urea rose from 44 mg. to 79 mg. per 100 ml., and the haematocrit level rose from 56 to 65 per cent. In spite of haemoconcentration there was

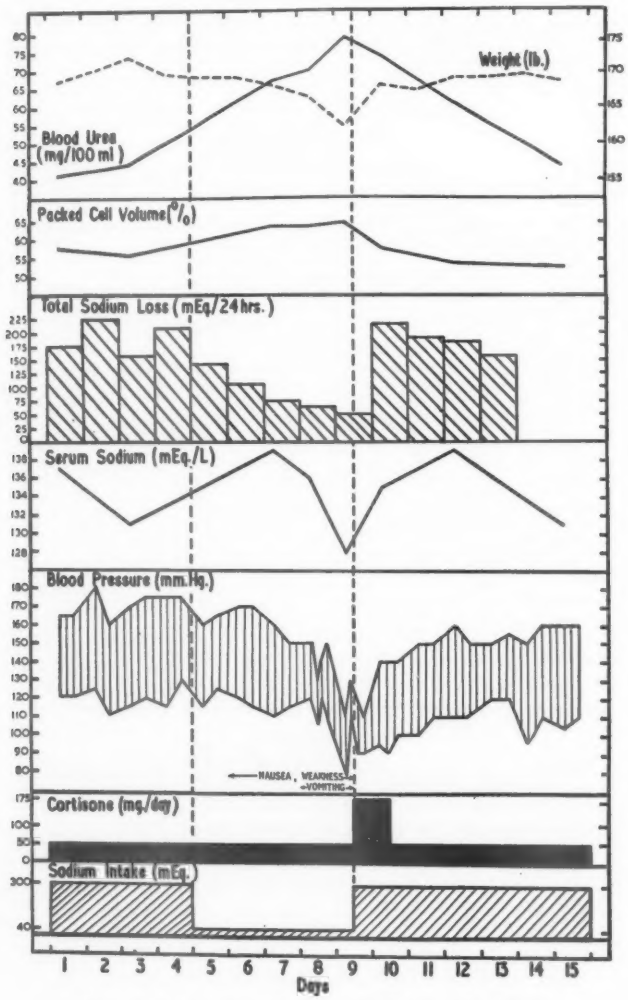

FIG. 2. Effect of reducing sodium intake in Case 4.

a slight fall in the level of serum-sodium. The total sodium loss fell from 150–230 mEq. a day to 56 mEq. on the fifth day. During this period his urinary output fell from 1,700 to 1,020 ml. a day, but he remained in negative fluid balance. He lost 7 lb. (3·18 kg.) in weight in five days. By the fifth day he showed the signs of an impending hypoadrenal crisis, and was given intravenous saline and hydrocortisone, after which he improved considerably.

Four of the five patients have died, but one is alive and working 24 months

after adrenalectomy (Table II). The average time of death was 15 months after operation, two patients dying of pontine haemorrhage, one of a ruptured dissection of the aorta, and one of a cerebral haemorrhage. Histological examination of the kidneys, both at operation and after death, showed the changes characteristic of hypertensive arteriolosclerosis. Patient No. 3 had chronic pyelonephritis in the right kidney. No evidence of any residual or accessory adrenal tissue was found in any of the patients.

Discussion

The results in this series are similar to those of Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt (1952) and Arnott (1956). Thorn and his colleagues described 15 cases of hypertension treated by total adrenalectomy alone. Eight of their patients had papilloedema, and can be classified as having had malignant hypertension. Only two of the eight were alive at the end of six months, and these two were still alive after 18 months. The blood-urea level was raised before operation in two of the eight patients, both of whom died within a month. Arnott has reported six cases of hypertension treated by total adrenalectomy alone. Five of these patients had papilloedema. Three of the five died, two a few days, and one just under two months, after operation. One patient was alive 12 months, and one 18 months, after adrenalectomy (personal communication).

It is important to assess these results in relation to the prognosis of untreated malignant hypertension, and also to the results of other forms of treatment (Fig. 3). Left untreated, only 21 per cent. of 146 patients with malignant hypertension were alive 12 months after diagnosis (Keith, Wagener, and Barker, 1939). After total adrenalectomy, 25 per cent. of the eight patients of Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt (1952), 40 per cent. of Arnott's five patients, and 60 per cent. of our five patients, survived for 12 months. At the end of two years, however, only one (20 per cent.) of our patients was alive, as were 12 per cent. of those untreated (Keith, Wagener, and Barker, 1939). Of the patients treated by sympathectomy, 40 per cent. of 143 with malignant hypertension were alive at the end of two years (Peet and Isberg, 1948). Using ganglion-blocking agents, McMichael (1956) had 50 per cent. of survivors among 34 cases of malignant hypertension after a similar period, but this group comprised only patients with an initial blood-urea level of 60 mg. per 100 ml. or less. McMichael's patients are therefore not strictly comparable to the others, except our own patients, in whom the initial blood-urea level was less than 40 mg. per 100 ml.

A striking feature in our patients was the well-being following adrenalectomy, and the regression of papilloedema, without any significant change in blood-pressure. Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt (1952) found that improvement in retinal vascular changes, and usually also clinical improvement, was correlated with a fall in blood-pressure; but they also encountered the phenomenon of symptomatic improvement without a

reduction in hypertension. The regression of papilloedema is difficult to explain. In four of our five cases the cerebrospinal-fluid pressure was over 200 mm. before operation. Other authors have reported similar findings in cases of hypertension with papilloedema. Shelburne, Blain, and O'Hare (1932) found a cerebrospinal-fluid pressure of over 200 mm. in 19 out of 20 cases, Schottstaedt

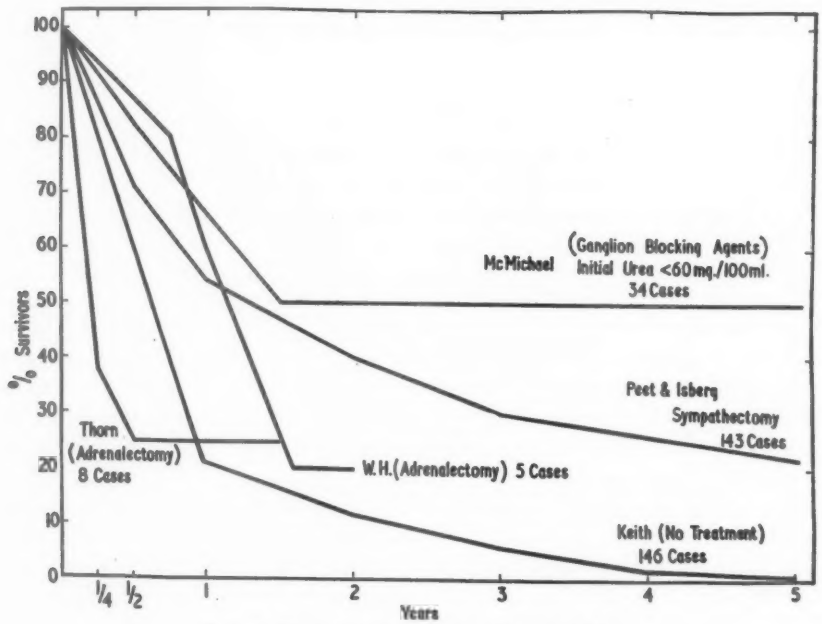

FIG. 3. Prognosis of malignant hypertension.

Keith = Keith, Wagener, and Barker (1939).
Peet and Isberg (1948).
Thorn = Thorn, Harrison, Merrill, Criscitiello, Frawley, and Finkenstaedt (1952).
McMichael (1956).
W.H. = Westminster Hospital (present series).

and Sokolow (1953) in 30 out of 48, and Revell, Borges, Yeager, Arnold, and Ahlquist (1954) in all 14 of their cases in which lumbar puncture was performed. Pickering (1952) found the cerebrospinal-fluid pressure to be over 250 mm. in 12 patients who had, or subsequently developed, 'albuminuric retinitis'. He found a statistical relation between the cerebrospinal-fluid and diastolic blood-pressures, and believed that neuroretinal oedema was due to raised intracranial pressure, although he was unable to account for the exceptions. In two of our patients (Cases 1 and 4), in whom the cerebrospinal-fluid pressure was measured after adrenalectomy and in whom there was complete regression of papilloedema, there was little change in cerebrospinal-fluid pressure or blood-pressure as compared with the levels before operation (Table I). Papilloedema may improve in the absence of specific treatment, even though hypertension persists, and in the course of 20 years Keith and Wagener (1951) collected 15 such cases. They believed that papilloedema is due to a 'decompensation of the circulation in the

optic nerve, retina, and choroid', rather than to the increased cerebrospinal-fluid pressure. It seems likely that in our patients the improvement was in some way due to treatment, although it is not clear how it occurred.

Our attempts to lower the blood-pressure after adrenalectomy by reducing replacement therapy with cortisone and salt were not successful. When the maintenance dose of cortisone was reduced in Case 3, the blood-urea level rose promptly, without any fall in blood-pressure. Rosenheim (1954) reported that one of his patients with hypertension, treated by total adrenalectomy, maintained a diastolic blood-pressure of 110 to 120 while chemically in a state of advanced Addisonian crisis. Arnott (1956) has claimed greater success than we had in lowering the blood-pressure by reducing the dose of cortisone, but it has been suggested (Hart, 1956) that this result may be due to the fact that his patients were women, whereas ours were all men. Patients with malignant hypertension respond less well to treatment with a low-sodium diet than do patients with benign hypertension. Perera (1955) restricted sodium intake to 250 mg. a day in six patients with malignant hypertension and intact adrenal glands. After 14 days there was no significant change in blood-pressure, whereas in uncomplicated primary hypertension a significant fall was induced. Although there was little change in the serum–sodium level in the uncomplicated cases of hypertension, it fell in the patients who had malignant hypertension. When, in Case 4, we restricted sodium to 1 gm. a day, while maintaining cortisone at 50 mg. a day, nausea and weakness developed within two days, and by the time the blood-pressure fell on the fifth day there was clinical and biochemical evidence of hypoadrenalism. In Perera's group of patients with malignant hypertension, in whom sodium had been restricted even more drastically, marked intolerance of salt restriction was not evident; this fact may be associated with the finding that the output of aldosterone is increased in malignant hypertensive patients with intact adrenal glands (Genest, 1955).

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Case Reports

Case 1. E. B., a jeweller aged 33 years (W.H. No. N5753). His mother had had a high blood-pressure, and his father had died of a stroke. In 1951 he had had a left external rectus palsy, at which time his blood-pressure was 140/85, and the cerebrospinal-fluid pressure was 300 mm., and 235 mm. when repeated. A left orchidectomy was performed for tuberculosis. He was readmitted to the Westminster Hospital on April 14, 1953 because of blurring of vision for three

months. His blood-pressure was 220/140, and papilloedema, haemorrhages, and exudates were present. There were no other abnormal physical signs. X-rays of the chest showed slight cardiac enlargement, and in the electrocardiogram there were signs of slight left ventricular hypertrophy. His urine contained a trace of protein, and could be concentrated to a specific gravity of 1,020 and diluted to 1,002. Urea clearance was 104 per cent. Two weeks after admission he had an epileptiform attack, and a week later a subarachnoid haemorrhage. Bilateral adrenalectomy was performed on May 5, 1953, after which he was maintained on 37·5 mg. of cortisone daily. He returned to work in November 1953, when he felt very well. He was readmitted in July 1954 because of nausea and weakness for three weeks, and cortisone was increased to 50 mg. daily. Papilloedema, haemorrhages, and exudates had cleared completely, but his blood-pressure was unchanged. He remained well until December 12, 1954, when he suddenly lost consciousness, and died 11 hours later. Post-mortem examination showed a pontine haemorrhage, hypertensive arteriolosclerosis in both kidneys, and an arterial thrombosis in one kidney.

Case 2. A. R., a joiner aged 48 years (W.H. No. Q12076). His father had died of a cerebral haemorrhage. He was admitted to the Westminster Hospital on December 12, 1953, because of deterioration in vision for six months. His blood-pressure was 205/145, and papilloedema, haemorrhages, and exudates were present, but there were no other abnormal physical signs. X-rays of the chest showed a normal-sized heart, and an electrocardiogram showed evidence of left ventricular hypertrophy. His urine contained a trace of protein, and could be concentrated to a specific gravity of 1,024 and diluted to 1,005. Bilateral adrenalectomy was performed in two stages on January 12 and 26, 1954, after which he was maintained on 50 mg. of cortisone daily. He returned to work in May 1954, feeling well apart from some lack of energy. Because of this symptom cortisone was increased to 75 mg. daily in June 1954. Papilloedema improved, although the disk edges remained blurred; haemorrhages and exudates cleared. There was no change in blood-pressure. On a routine visit to hospital on November 2, 1954 he collapsed, lost consciousness, and died. Post-mortem examination showed a pontine haemorrhage, and the kidneys showed hypertensive arteriolosclerosis.

Case 3. Y. W., a compositor aged 26 years (W.H. No. M11599). There was no relevant family history. In 1951 he had a right external rectus palsy, and his blood-pressure was 200/140 and cerebrospinal-fluid pressure 250 mm. He was treated with hexamethonium for six months. He remained hypertensive, but otherwise well, until he was readmitted to the Westminster Hospital on March 12, 1954, because of haematuria. Haematuria cleared after admission, but he developed severe headaches and vomiting, and papilloedema, haemorrhages, and exudates all appeared in the course of six weeks while he was in the ward. His blood-pressure was 215/155, and there was slight cardiac enlargement, confirmed by X-rays, but no other abnormal physical signs. An electrocardiogram showed evidence of gross left ventricular hypertrophy. His urine, after haematuria had stopped, contained only a trace of protein, and could be concentrated to a specific gravity of 1,022 and diluted to 1,002. Urea clearance was 112 per cent. Intravenous pyelography showed that the right kidney was smaller than the left, and an aortogram showed that it had a decreased blood-supply. Bilateral adrenalectomy was performed in two stages on May 4 and 20, 1954, after which the patient was maintained on 50 mg. of cortisone daily. He returned to work in October 1954 feeling well; the papilloedema had improved, and the haemorrhages had cleared. In November 1954 headaches returned, and

he was readmitted on December 17, 1954, when his blood-pressure was 230/170, and papilloedema and haemorrhages were again present. After an unsuccessful attempt to lower his blood-pressure by reducing cortisone dosage (see pp. 152–3), he was treated with hexamethonium, and later pentolinium, by injection. His blood-pressure was only slightly reduced, but he felt better, and his fundi improved. He returned to work in July 1955, and remained well until he was readmitted on November 19, 1955, with severe pains in the chest and back. A diagnosis of dissection of the aorta was made. He died suddenly on December 20, 1955, and post-mortem examination showed an extensive dissection of the aorta, which had ruptured into the left pleural cavity. The right kidney weighed 57 gm., and showed chronic pyelonephritis and an old arterial thrombosis. The left kidney weighed 198 gm., and showed hypertensive arteriolosclerosis only.

Case 4. F. W., a salesman aged 54 years (W.H. No. R7163). A sister had died of coronary thrombosis at 70 years. In 1934 his blood-pressure was 160/100, and in 1952 it was 260/150. He had had daily headaches since 1952, and in May 1954 he had an episode of confusion and dysphasia, after which his vision deteriorated. He was admitted to the Westminster Hospital on July 19, 1954, at which time he had slight nominal aphasia, a blood-pressure of 200/130, and papilloedema, haemorrhages, and exudates. There were no other abnormal physical signs. The size of the heart on X-ray was normal, and an electrocardiogram showed evidence of slight left ventricular hypertrophy only. His urine contained a trace of protein, and could be concentrated to a specific gravity of 1,022 and diluted to 1,002. Urea clearance was 78 per cent. Bilateral adrenalectomy was performed in two stages on August 9 and 23, 1954, after which he was maintained on 50 mg. of cortisone daily. He started work in December 1954, and was well apart from some left-sided headaches. On May 27, 1955, he was admitted to St. Mary's Hospital, Newport, Isle of Wight, under the care of Dr. J. C. Harland, after an attack of mental confusion, and had right facial weakness; he was considered to have had a cerebrovascular accident. On October 8, 1955, he was admitted to the Westminster Hospital after an epileptiform fit, and was found to have a partial right homonymous hemianopia and signs of a left parietal lesion, presumed to be vascular. He returned to work in December 1955. As his blood-pressure remained raised, he was readmitted on April 6, 1956 so that the effect of reducing sodium intake might be studied. Hypoadrenalism developed before his blood-pressure fell (see pp. 153–4). Subsequently he was working part-time, and was well, apart from left-sided headaches; his blood-pressure was 190/130, and the fundi were normal apart from the narrowing of the arteries. He was last seen in August 1956.

Case 5. J. L., a railway porter aged 57 years (W.H. No. 7933). There was no relevant family history. He was previously well, apart from a duodenal ulcer. He was admitted to the Westminster Hospital on August 13, 1954, because of deterioration in vision for four months and an epileptiform attack two weeks before admission. His blood-pressure was 175/120, and papilloedema, haemorrhages, and exudates were present, but there were no other abnormal physical signs. The size of the heart on X-ray was normal, and an electrocardiogram showed moderate left ventricular hypertrophy. His urine was normal, and could be concentrated to a specific gravity of 1,020 and diluted to 1,002. Left adrenalectomy was performed on September 14, 1954; the right adrenal was removed on November 26, 1954, as he was not at first willing to have the second operation. He was maintained on 50 mg. of cortisone daily, and started light work in February 1955. His blood-pressure remained unchanged, although the papilloedema, haemorrhages, and exudates cleared. He remained well, until

he collapsed at work and was admitted to University College Hospital, under the care of Professor M. Rosenheim, on September 30, 1955, where he died the same day. Post-mortem examination revealed a large left cerebral haemorrhage; the kidneys showed hypertensive arteriolosclerosis only.

Summary

The rationale and history of adrenalectomy for hypertension are briefly reviewed.

Five patients with malignant hypertension and good renal function have been treated by total adrenalectomy. The operation was performed without difficulty, and the patients were subsequently maintained on cortisone alone.

Papilloedema improved in all cases, and all the patients returned to work. In none was there any significant reduction of blood-pressure. When further attempts were made to lower the blood-pressure, by reducing either the cortisone dosage or the salt intake, the patients showed signs of hypoadrenalism before there was any reduction in blood-pressure. The relation of blood-pressure to papilloedema and cerebrospinal-fluid pressure in malignant hypertension is discussed.

All the patients derived symptomatic benefit from adrenalectomy, but there is no evidence that their lives were prolonged.

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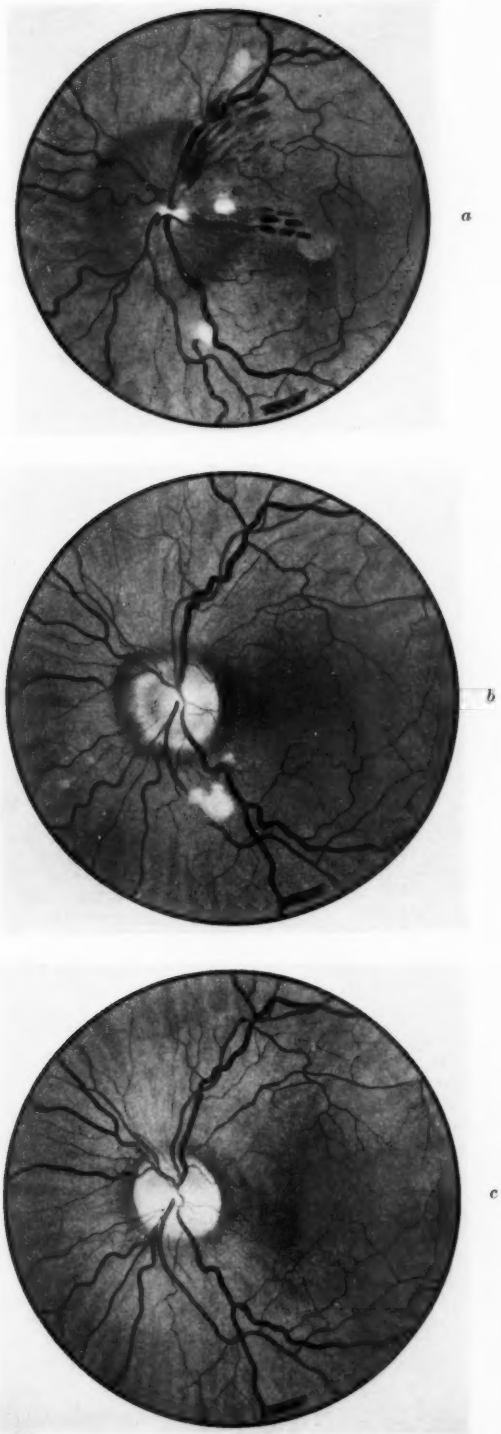

FIG. 4. Case 3. Fundus paintings: (*a*) before treatment; (*b*) 6 months after adrenalectomy; (*c*) 17 months after adrenalectomy and after 9 months of treatment with pentolinium

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